Non-Invasive Ventilation and NIV-NAVA in Preterm Infants: a Prospective Observational Cohort Study

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Keywords

Preterm infant ; noninvasive ventilation ; interactive ventilatory support ; bronchopulmonary dysplasia ; prospective studies.

Abstract

Objective

To study the use of non-invasive ventilation (NIV), and in particular non-invasive neurally adjusted ventilatory assist (NIV-NAVA) in our neonatal intensive care unit (NICU), assessing its feasibility, safety and outcome.

Methods

We conducted a prospective, single-centre observational cohort study, enrolling preterm infants who received at least 24 hours of NIV. Primary endpoints were indication and duration of various NIV modes. Secondary endpoints included significant adverse events such as complications, treatment failure, and the incidence of bronchopulmonary dysplasia (BPD).

Results

Sixty-eight infants were included, with a median gestational age (GA) of 31.3 weeks (IQR 29-32.7) and a median birth weight of 1475 g (IQR 1110-1850). Among them, 36 infants received NIV-NAVA, predominantly as primary support (69.4%). Infants receiving NIV-NAVA had a mean LUS-score at inclusion of 8.6 (SD 2.4, range 3-12) and a median duration of NIV of 32 days (IQR 16.3-65.8). We observed 1 case of pneumothorax and 1 case of pulmonary haemorrhage. The treatment failure rate among infants receiving NIV-NAVA was 22.2%, increasing to 45.5% in extremely premature infants. BPD was diagnosed in 9 (15%) infants.

Conclusion

This study is one of the first prospective trials studying all NIV modes including NIV-NAVA from birth to NICU discharge. Our findings illustrate the feasibility and safety of NIV-NAVA across various ranges of GA, despite higher failure rates in extremely preterm infants. The incidence of BPD among our study population was 15%.

Introduction

Bronchopulmonary dysplasia (BPD) remains a common and severe complication in preterm infants, particularly those born at 28 weeks' gestational age (GA) or less (1,2). Despite substantial progress in perinatal care, the incidence of BPD has not declined (1-3). Initially attributed to aggressive mechanical ventilation and high oxygen exposure ('old BPD'), it has evolved into a condition characterised by impaired alveolar development and pulmonary vascular dysregulation ('new BPD') (1,4,5).

Treatment strategies for BPD primarily focus on minimizing lung injury by avoiding invasive ventilation (1). Non-invasive neurally adjusted ventilatory assist (NIV-NAVA) is a form of non-invasive positive pressure ventilation (NIPPV) that delivers synchronised, proportionally assisted ventilatory support using the diaphragm's electrical activity (Edi), offering comfortable and potentially lung-protective support (6). A recent meta-analysis found no difference in treatment failure or adverse events between NIV-NAVA and nasal continuous positive airway pressure (nCPAP) in preterm infants (7). According to a review by Shi et al., some studies on NIV-NAVA have shown promising results, with improved synchronisation compared to NIPPV and a reduced need for intubation in comparison to nCPAP (8). However, both studies concluded that limited data and low-certainty evidence currently prevent a clear determination of NIV-NAVA's effectiveness and safety (7,8).

Following a small exploratory study on NIV-NAVA in our unit, we initiated a more comprehensive study on its use in preterm infants (9). Our aim is to investigate the feasibility and safety of NIV-NAVA alongside other non-invasive ventilation (NIV) modes.

Methods

Study design

This prospective, single-centre observational cohort study was conducted at the neonatal intensive care unit (NICU) of the University Hospital of Brussels.

Inclusion

All neonates admitted to our NICU between February 2023 and January 2024 were screened for inclusion. Eligible infants were those born before 37 weeks' gestation and requiring at least 24 hours of NIV, including (heated humidified) high flow nasal cannula ((HH)HFNC), nCPAP or NIV-NAVA. Infants with major congenital pathology were excluded.

Respiratory support strategy

In our unit, preterm infants diagnosed with respiratory distress syndrome (RDS) are primarily supported with nCPAP or NIV-NAVA. Extremely preterm infants, born before 28 weeks' gestation, generally receive NIV-NAVA, while those born at or after 28 weeks' gestation typically begin with nCPAP. NIV-NAVA is also used as a weaning mode following extubation, in cases of nCPAP failure and during less invasive surfactant administration (LISA). nCPAP is often used after weaning from NIV-NAVA, while HHHFNC is mainly used in the later stages of weaning.

Generally, the following settings are employed: positive end expiratory pressure (PEEP) ranging from 4 to 8 cmH_2O, NAVA levels between 0

and 2.5 $cmH_2O/\mu V$ and titrated to achieve normal Edi-peak values of 5 to 15 µV, apnoea time between 2 and 5 seconds, back-up frequency of 40 to 55 per minute and back-up pressure above PEEP (PAP) between 5 and 10 cmH_2O. Saturation targets for oxygen therapy are set at 90 to 95% (10). Continuous transcutaneous carbon dioxide monitoring is used as often as possible, and lung ultrasounds, particularly using the lung ultrasound score (LUS), are routinely performed (11).

Table 1: BPD definition according to NICHD consensus (Values are percents).

Grades	Invasive IPPV*	NCPAP, NIPPV, nasal cannula ≥ 3 L/min	Nasal cannula flow of 1 - <3 L/min	Hood O_2	Nasal cannula flow of < 1L/min
I	/	21	22-29	22-29	22-70
II	21	22-29	≥ 30	≥ 30	≥ 70
III	> 21	≥ 30			
IIIa	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (e.g. necrotising enterocolitis, intraventricular haemorrhage, redirection of care, episodes of sepsis, …)				

* Excluding infants ventilated for primary airway disease or central respiratory control conditions

Invasive ventilation is initiated if non-invasive methods fail to adequately support the infant, with a preference for invasive NAVA. If this is not feasible, alternative modes such as volume-controlled conventional ventilation or high frequency oscillation ventilation are used.

All infants on NIV-NAVA or invasive ventilation were ventilated with a Servo-n ventilator (Getinge, Sweden, System version 2.01). nCPAP is delivered by a Servo-n ventilator or by a bubble CPAP system (Fisher and Paykel®). For all infants, the Flexitrunk™ nasal interface (Fisher and Paykel®) was employed, alternating binasal prongs and nasal mask. HFNC is delivered by the Optiflow™ system (Fisher and Paykel®).

Caffeine is initiated for all infants born at a gestational age of 32 weeks or less, and for older infants experiencing frequent or severe apnoeas. A loading dose of 10 mg/kg is given as soon as possible, followed by a maintenance dose of 2.5 to 5 mg/kg/day initiated 24 hours later. During the NIV study, our unit participated in the DOXA-trial, where infants with severe and persistent apnoeas on NIV and at risk of reintubation were randomly assigned, following parental consent, to receive either placebo or doxapram in a double-blinded fashion (12).

Infants requiring invasive ventilation beyond the first week of life are eligible for corticosteroid treatment with dexamethasone to facilitate extubation. Typically, a low-dose regimen, consistent with the DART study protocol, is used, with a total cumulative dose of 0,9 mg/kg (13). For those experiencing severe side-effects or requiring prolonged treatment, an individualised dosing scheme is applied with a maximum cumulative dose set at 4 mg/kg to avoid the risk of cerebral palsy (14).

All preterm infants requiring intubation at birth promptly receive surfactant, usually within the first hour of life. For others, early selective surfactant administration is used, utilising a fraction of inspired oxygen (FiO_2) > 0.3 or a LUS-score > 8 (10,15). Surfactant is administered via the LISA procedure whenever feasible, with an initial dose of 200 mg/kg and subsequent doses of 100 mg/kg. During the LISA procedure, infants are supported with NIV-NAVA while being sedated with propofol.

Outcomes

The primary objective of this study is to evaluate the use of NIV in our NICU, with a particular focus on NIV-NAVA, assessing its feasibility and safety. Primary endpoints include the duration and indications of various NIV support modes. Secondary endpoints encompass adverse events, including complications, treatment failure, the incidence of BPD and the need for prolonged oxygen therapy at home.

A mode is considered 'failed' if a transition to a higher level of respiratory support is required, such as from HFNC to nCPAP or NIV-NAVA, from CPAP to NIV-NAVA or if intubation is necessary. The escalation of respiratory support, as determined by the attending physician, typically occurs when there is a PCO_2 exceeding 60-65 mmHg with a pH below 7.2, an FiO_2 surpassing 40%, or frequent apnoea despite maximal settings for the chosen support mode.

BPD is defined according to the 2018 National Institute of Child Health and Human Development (NICHD) criteria. A premature infant (<32 weeks' GA) with BPD has persistent parenchymal lung disease, radiographic confirmation of parenchymal lung disease, and at 36 weeks of post-menstrual age requires 1 of the following FiO_2 ranges/oxygen levels/ O_2 concentrations for ≥ 3 consecutive days to maintain arterial oxygen saturation in the 90-95% range, as shown in Table 1 (16).

Infants requiring prolonged oxygen therapy at home, despite not meeting the criteria for BPD as mentioned above, were retrospectively classified as having BPD.

Data collection

Prospective data collection involved chart review and daily extraction of blood gases and ventilatory data on a fixed time point. All gathered data were exported into an Excel file. Lung ultrasound was performed regularly using a high-frequency linear probe (Esaote MyLab twice®). Data collection stopped at discharge from the NICU.

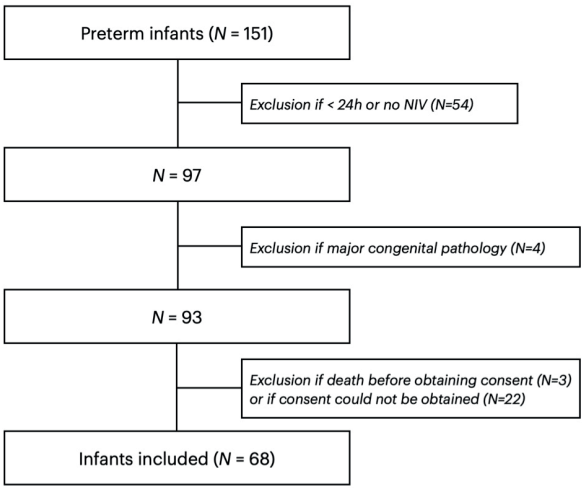
Statistical analysis

Descriptive statistics were conducted to summarize the characteristics of all participants. Continuous variables are reported as either medians with interquartile ranges (IQR) or means with standard deviations (SD) and ranges, depending on their distribution. Categorical variables are presented as counts (n) and percentages (%). The normality of continuous variables was assessed through visual inspection, skewness and kurtosis analysis, and the Shapiro-Wilk test. Continuous variables were analysed using the independent t-test and Mann–Whitney U test as appropriate. A p-value < 0.05 was considered to be statistically significant. Boxplots were used to visually represent the distribution of continuous variables. Statistical analysis was carried out using SPSS, version 29 (IBM, US).

Ethical approval

The study protocol was approved by the UZ Brussel Medical Ethics Committee and prospectively registered on ClinicalTrials.gov (https://clinicaltrials.gov ; NCT05987800). Signed written consent by the parents was obtained prior to inclusion.

Figure 1: Flowchart of inclusion.



Results

Inclusion

During the study period, 151 preterm infants were admitted to our unit, with 97 meeting the eligibility criteria. Of these, 68 infants were ultimately included. Figure 1 outlines the inclusion process in detail.

Baseline characteristics

The median gestational age at birth was 31.3 weeks (IQR 29-32.7), with 12 (17.6%) infants born before 28 weeks' gestation. The median birth weight was 1475 g (IQR 1110-1850). Detailed baseline characteristics are provided in Table 2.

Primary endpoints

General overview

Respiratory distress syndrome (RDS) was the primary reason for initiating NIV in 63 (92.6%) infants. At the time of inclusion, 40 (58.8%) infants were supported with nCPAP, while 28 (41.2%) infants received NIV-NAVA. The mean LUS-score at inclusion was 7.9, (SD 2.6, range 2 - 12). Surfactant was administered to 29 (42.6%) infants, with 23 infants receiving their first dose via LISA. Invasive ventilation was required in 10 (14.7%) infants, and the median duration of NIV was 13.5 days (IQR 6-38.5).

Important differences in the duration of respiratory support were observed across GA groups. Infants born at a GA between 24 and 27 6/7 weeks had a median NIV duration of 65.5 days (IQR 51.3-74), significantly longer than those born between 28 and 31 6/7 weeks, with a median duration of 20 days (IQR 8-33) ($p < 0.05$), and those born between 32 and 36 6/7 weeks ($p < 0.05$), with a median duration of 6 days (IQR 3.5-13). Furthermore, a significant difference was found between the latter two groups ($p < 0.05$). A detailed overview of these primary endpoints is presented in Table 3.

Table 2: Baseline characteristics.

Characteristics	*N* = 68
GA at birth, median weeks (IQR)	31.3 (29-32.7)
- 24 - 27 6/7 weeks, *n (%)* - 28 - 31 6/7 weeks, *n (%)* - 32 - 36 6/7 weeks, *n (%)*	12 (17.6) 27 (39.7) 29 (42.6)
Birth weight, median g (IQR)	1475 (1110-1850)
Male/female, *n/n*	38/30
Antenatal steroids, *n (%)*	52 (76.5)
Caesarean delivery, *n (%)*	51 (75)
Chorioamnionitis, *n (%)*	5 (7.6)
Caffeine, *n (%)*	53 (77.9)

Table 3: Detailed overview of primary endpoints.

Characteristics	All participants *N* = 68	GA 24 - 27 6/7 weeks (*N* = 12)	GA 28 - 31 6/7 weeks (*N* = 27)	GA 32 - 36 6/7 weeks (*N* = 29)
Reason for respiratory support - RDS, *n (%)* - TTN, *n (%)*	 63 (92.6) 5 (7.4)	 12 (100)	 27 (100)	 24 (82.8) 5 (17.2)
Respiratory support at inclusion				
Mode - nCPAP, *n (%)* - NIV-NAVA, *n (%)*	 40 (58.8) 28 (41.2)	 1 (8.3) 11 (91.7)	 17 (63) 10 (37)	 22 (75.9) 7 (24.1)
Indication - Primary support, *n (%)* - Post-extubation, *n (%)*	 65 (95.6) 3 (4.4)	 10 (83.3) 2 (16.7)	 26 (96.3) 1 (3.7)	 29 (100)
LUS-score at inclusion, mean (SD, range)	7.9 (2.6, 2-12) (*N*=40)	10 (6-12) [a] (*N*=9)	7.33 (2, 3-10) (*N*=15)	7.8 (2.5, 3-12) (*N*=16)
Surfactant, n (%)	29 (42.6)	10 (83.3)	11 (40.7)	8 (27.6)
Amount - One dose, *n* - Two doses, *n* - Three doses, *n*	 22 4 3	 5 3 2	 9 1 1	 8 0 0
Administration initial dose - LISA, *n* - INSURE, *n* - Endotracheal tube, *n*	 23 2 4	 8 2	 9 1 1	 6 1 1
Doxapram	1	1		
DOXA-trial study medication	1	1		
Total duration, median days (IQR)	14.5 (6-45.5)	74 (55, 87.5)	20 (8-34)	6 (3.5-13.5)
Duration of - Invasive support, median days (IQR) - NIV, median days (IQR) - NIV-NAVA, median days (IQR) - nCPAP, median days (IQR) - HFNC, median days (IQR)	 10 (14.7)[b] 13.5 (6-38.5) 1 (0-5) 4 (2.3-8) 7 (2.3-15)	 0.5 (0-16.8) 65.5 (51.3-74) 33 (6.8-41.8) 20 (10-31.5) 12 (7.5-25.8)	 2 (7.4) b 20 (8-33) 1 (0-3) 4 (3-8) 13 (3-20)	 2 (6.9) b 6 (3.5-13) 0 (0-3) 3 (1.5-5) 3 (0-8)

[a] represented as median (IQR)
[b] represented as number of infants receiving invasive support ((number of infants receiving IV)/(total number of infants in this category)%)

Table 4: Comparison of characteristics of infants with and without NIV-NAVA.

Characteristics	NIV-NAVA (*N*=36)	No NIV-NAVA (*N*=32)	*p*-value
GA at birth, mean weeks (SD, range)	29.6 (27.5-32) [a]	32.2 (1.8, 27-35 4/7)	< 0.05
- 24 - 27 6/7 weeks, *n (%)*	11	1	
- 28 - 31 6/7 weeks, *n (%)*	15	12	
- 32 - 36 6/7 weeks, *n (%)*	10	19	
Birth weight, mean g (SD, range)	1245 (914-1750) [a]	1711 (438, 903-2795)	< 0.05
Male/female, n/n	22/14	16/16	
Antenatal steroids, *n (%)*	28 (77.8)	24 (75)	
Caesarean delivery, *n (%)*	27 (75)	24 (75)	
Chorioamnionitis, *n (%)*	2 (5.9)	3 (9.4)	
LUS-score at inclusion, mean (SD, range)	8.6 (2.4, 3-12) (*N*=26)	6.5 (2.6, 5.5-7.5) (*N*=14)	< 0.05
Surfactant, *n (%)*	25 (69.4)	4 (12.5)	
Amount			
- One dose, *n*	18	4	
- Two doses, *n*	4	/	
- Three doses, *n*	3	/	
Administration initial dose			
- LISA, *n*	20	3	
- INSURE, *n*	1	1	
- Endotracheal tube, *n*	4		
Total duration of NIV, median days (IQR)	32 (16.3-65.8)	6.5 (3.3-11.8)	< 0.05

[a] data represented as median (IQR)

NIV-NAVA

Of the 68 infants included in the study, 36 (52.9%) received NIV-NAVA. These infants were born at a significantly lower median GA of 29.6 (IQR 27.5-32) weeks, compared to those who received only nCPAP and/or HFNC ($p < 0.05$). The median birth weight of infants receiving NIV-NAVA was 1245 grams (IQR 914-1750). For this group, the mean LUS-score at inclusion was 8.6 (SD 2.4, range 3-12). The median total duration of NIV in infants treated with NIV-NAVA was 32 days (IQR 16.3-65), contrasting to 6.5 days (IQR 3.3-11.8) for those only receiving nCPAP and/or HFNC. For a detailed comparison between the two groups, please refer to Table 4.

The majority of infants receiving NIV-NAVA, totalling 25 (69.4%) infants, were supported with NIV-NAVA as their primary mode of respiratory support, while 6 (16.7%) were transitioned to NIV-NAVA following nCPAP failure. The median duration of NIV-NAVA was 4.5 days (IQR 3-28.3). Stratification by GA revealed notable differences in NIV-NAVA duration. Infants born between 24 and 27 6/7 weeks of GA had a significantly longer median duration of 37 days (IQR 9-42), compared to both the 28 to 31 6/7 weeks GA group ($p<0.05$) and the 32 to 36 6/7 weeks

Table 5: Indication, duration and baseline settings of NIV-NAVA, nCPAP and HFNC.

Characteristics	NIV-NAVA (*N*=36)	nCPAP (*N*=65)	HFNC (*N*=58)
Indication first use			
- Primary support mode, n (%)	25 (69.4)	40 (61.5)	
- Weaning mode, n (%)	3 (8.3)	24 (36.9)	52 (89.7)
- Weaning failure, n (%)		1 (1.5)	6 (10.3)
- nCPAP failure, n (%)	6 (16.7)		
- HFNC failure during sepsis, n (%)	2 (5.6)		
Settings at inclusion			
NIV-NAVA			
- Level, median cmH2O/µV (IQR)	1.5 (1.2-1.8)		
- PEEP, median cmH2O (IQR)	7 (7-8)		
- FiO2, median % (IQR)	26 (21-35)		
- Apnoea time, median seconds (IQR)	3 (2-3)		
- Back-up PAP, median cmH2O (IQR)	7 (5-8)		
- Back-up frequency, median per minute (IQR)	50 (45-50)		
CPAP			
- PEEP, median cmH2O (IQR)		6.5 (6-7)	
- FiO2, median % (IQR)		21 (21-24)	
HFNC			
- Flow, median L/min (IQR)			4 (3.8-5)
- FiO2, median % (IQR)			21 (21-21)
(Duration of respective modes, median days (IQR)			
Total	4.5 (3-28.3)	4 (3-8.5)	9.5 (4.8-16.8)
- 24 - 27 6/7 weeks	37 (9-42) (*N*=11)	20 (10-31.5) (*N*=12)	12 (7.5-25.8) (*N*=12)
- 28 - 31 6/7 weeks	3 (2-18) (*N*=15)	4 (3-8) (*N*=24)	14 (5-20.5) (*N*=25)
- 32 - 36 6/7 weeks	3 (3-5) (*N*=10)	3 (1.5-5) (*N*=29)	6 (3-11) (*N*=21)

GA group (p<0.05). However, no significant difference was observed between infants born at 28 to 31 6/7 weeks and those born at 32 to 36 6/7 weeks (p=0.919). Table 5 provides a detailed overview of these findings, including the NIV-NAVA settings at inclusion, while figure 2 offers a visual representation.

NCPAP

In our cohort, 65 (95.5%) infants received nCPAP at some point during their NICU stay. For 40 (61.5%) infants, nCPAP was the primary mode of respiratory support, while 24 (36.9%) used it as part of their weaning process from NIV-NAVA. Only 1 (1.5%) infant required nCPAP after HFNC failure. The overall median duration of nCPAP for all infants was 4 days (IQR 3-8.5), while infants born between 24 and 27 6/7 weeks of GA had a median duration of 20 days (IQR 10-31.5). These results, along with the nCPAP settings at inclusion, are summarised in Table 5.

HFNC

Out of the 68 infants analysed, 58 (85.3%) received HFNC. Among them, 52 (89.7%) were initiated on HFNC following weaning from nCPAP and/or NIV-NAVA. Six (10.3%) infants got HFNC for the first time after weaning failure, when the discontinuation of NIV directly from nCPAP failed. The overall median duration of HFNC for all infants was 9.5 days (IQR 4.8-16.8). Infants born between 24 and 27 6/7 weeks of GA had a median HFNC duration of 12 days (IQR 7.5-25.8). A detailed summary, along with the HFNC settings at initiation, can be found in Table 5.

Secondary endpoints

Adverse events

Among the 36 infants treated with NIV-NAVA, 1 developed a pneumothorax, and another 1 had a pulmonary haemorrhage. No other adverse events, such as spontaneous intestinal perforation, were observed. Additionally, no adverse events were reported during the use of nCPAP or HFNC. There was no mortality in our study population.

Treatment failure

Out of the 36 infants treated with NIV-NAVA, 8 (22.2%) experienced treatment failure. The causes included oxygenation failure in 3 infants, hypercapnia in 1, combined hypercapnia and oxygenation failure in another 1, severe apnoea in 2, and acute collapse during pulmonary haemorrhage in 1. Among infants with a GA between 24 and 27 6/7 weeks, treatment failure occurred in 5 out of 11 cases (45.5%). For those born between 28 and 31 6/7 weeks, treatment failure was observed in 2 out of 15 (13.3%), while in infants between 32 and 36 6/7 weeks, the rate was 1 out of 10 cases (10%). The median NIV-NAVA settings prior to reintubation were: NIV-NAVA level of 2 $cmH_2O/\mu V$ (IQR 1.3-2), PEEP of 7 cmH_2O (IQR 7-8.8) and FiO_2 of 32.5% (IQR 21 - 55).

In the cohort of 65 infants who received nCPAP, 8 (12.3%) experienced treatment failure. The failures included hypercapnia in 3 infants, oxygenation failure in 1, combined hypercapnia and oxygenation failure in 1, severe apnoea in 2, and increased work of breathing in 1. Among the 55 infants who received HFNC, only 1 (1.8%) experienced treatment failure, which was attributed to hypercapnia.

Length of NICU stay

The median duration of NICU stay for all infants in the study was 27 days (IQR 15.3-53). Infants receiving NIV-NAVA had a median NICU stay of 46.5 days (IQR 23.3-77).

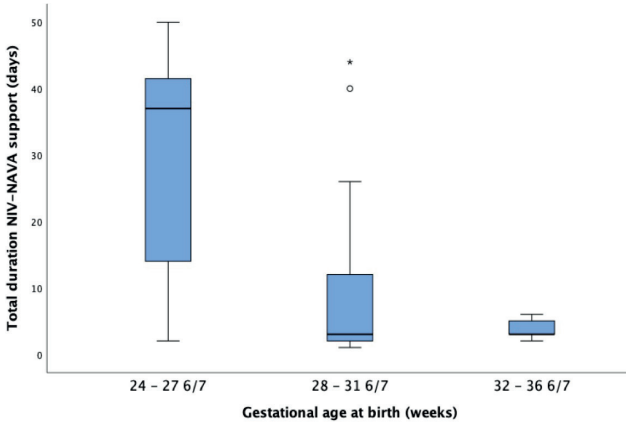
Use of corticosteroid treatment

Out of the 68 infants, 6 (8.8%) were treated with systemic corticosteroids.

Bronchopulmonary dysplasia

Of the 68 infants, data for assessing BPD were available for 60 infants, as some were transferred to secondary-level hospitals before data collection was completed. Among these infants, 8 (13.3%) were diagnosed with grade I BPD, and 1 (1.7%) with grade 2 BPD. The overall incidence of BPD among the 31 infants who received NIV-NAVA was 29%.

Figure 2: Differences in duration of NIV-NAVA across groups of different GA receiving NIV-NAVA.



Since BPD is defined as occurring in infants born before 32 weeks of GA, our comparison between infants with and without BPD focuses exclusively on neonates younger than 32 weeks GA. This resulted in 39 eligible neonates, with outcome data available for 32 of them.

Infants diagnosed with BPD had a lower, though not statistically significant, mean GA at birth, of 27.5 weeks (SD 1.2, range 26-29.1), and a significantly lower mean birth weight of 891 g (SD 257, range 510-1300), compared to those without BPD. The mean LUS-score at inclusion was 9.6 (SD 1.7, range 7-12) for infants with BPD, compared to 7.3 (SD 3, range 2-12) for those without, although this difference was not statistically significant. The median duration of NIV was 66.5 days (IQR 65-71.8) for infants with BPD, compared to 21 days (IQR 8-57.8) for those without BPD. A detailed comparison between infants with and without BPD is presented in table 6.

Home support

Since our centre provides follow-up for all infants requiring respiratory support after discharge, we were able to analyse data from 68 infants. Of these, 1 infant required nCPAP at discharge, and 2 needed home oxygen therapy.

Discussion

Our research is among the first prospective observational studies to investigate NIV-NAVA in preterm infants. Unlike the few existing prospective studies on NIV-NAVA, which are primarily interventional and focus on comparing NIV-NAVA with nCPAP in controlled clinical settings, our study is purely observational and descriptive (17-20). It documents local practices from birth to discharge, across all gestational ages. While our study did not directly compare NIV-NAVA with other modes of NIV, it provides valuable insights into its feasibility, safety and practical application in everyday clinical settings.

Previous studies by Kallio et al., Lee et al. and Yagui et al., focused on comparing NIV-NAVA with nCPAP as the primary respiratory support mode, while Shin et al. focused solely on infants receiving NIV-NAVA after extubation (17-20) These studies had varying inclusion criteria, some recruited only infants with a GA above 28 weeks, while others specifically included infants with a GA below 30 weeks or a birth weight below 1500 grams (17-20). In contrast, our study is the first to include preterm infants across all GA, using NIV-NAVA both as the primary support mode, post-extubation and after nCPAP failure.

In our study, 36 infants received NIV-NAVA. These infants had a significantly lower median gestational age of 29.6 weeks (IQR 27.5-32) and a significantly lower median birth weight of 1245 g (IQR 914-1750) compared to those not receiving NIV-NAVA. The median duration of NIV-NAVA was 4.5 days (IQR 3-28.3), with infants born below 28 weeks of GA had a notably longer median duration of 37 days (9-42). These infants had more severe RDS, reflected in higher surfactant requirements, longer durations of NIV and higher LUS scores.

Table 6: Comparison of characteristics of infants with and without BPD.

Characteristics	BPD (*N*=8)	No BPD (*N*=24)	*p*-value
Degree of BPD - Grade I - Grade II - Grade III	 7 1		
GA at birth, median weeks (IQR) - 24 - 27 6/7 weeks, *n (%)* - 28 - 31 6/7 weeks, *n (%)*	27.5 (1.2, 26-29.1)[a] 4 (50) 4 (50)	29.9 (27.1-31.3) 8 (33.3) 16 (66.7)	0.061
Birth weight, mean g (SD, range)	891 (257, 510-1300)	1274 (418, 427-1896)	< 0.05
Male/female, *n/n*	6/2	13/11	
Antenatal steroids, *n (%)*	7 (87.5)	20 (83.3)	
Caesarean delivery, *n (%)*	7 (87.5)	17 (70.8)	
Chorioamnionitis, *n (%)*	1 (12.5)	4 (16.7)	
LLUS-score at inclusion, mean (SD, range)	9.6 (1.7, 7-12) (*N=7*)	7.3 (3, 2-12) (*N=14*)	0.077
Surfactant, *n (%)* Amount - One dose, *n* - Two doses, *n* - Three doses, *n* Administration initial dose - LISA, *n* - INSURE, *n* - Endotracheal tube, *n*	7 (87.5)) 4 1 2 7 0 0	10 (41.7) 6 3 1 8 0 2	
Total duration respiratory support, median days (IQR) Duration of - Invasive support, median days (IQR) - NIV, median days (IQR) - NIV-NAVA, median days (IQR) - nCPAP, median days (IQR) - HFNC, median days (IQR)	81.6 (20.2,53-114)[a] 4.5 (0-20.5) 66 .5(65-71.8) 32.5 (7-41.5) 22.6 (8.7,10-35)[a] 11 (7.5-14.5)	21 (8-64.8) 4 (16.7)[b] 21 (8-57.8) 2 (0-15.8) 5 (3-10) 11.5 (5-22.5)	< 0.05 < 0.05 < 0.05 < 0.05 < 0.05 0.695
Corticosteroid treatment, *n (%)*	5 (62.5%)	1 (4.2%)	
Home therapy, *n (%)* nCPAP Oxygen	 1 (12.5) 2 (25)		
Failure of NIV-NAVA, *n (%)*	4 (50)	3 (23.1) (*N=13*)	
Length of NICU stay, median days (IQR)	83.8 (19.5, 54-115) a	39 (22-71.3)	< 0.05

[a] data represented as mean (SD, range)
[b] represented as number of infants receiving invasive support ((*number of infants receiving IV*)/(*total number of infants in this category*)%)

When examining the total duration of NIV in infants receiving NIV-NAVA, the median was 32 days (IQR 16.3-65.8), similar to the 35.5 days (IQR 9.8-44.8) reported by Lee et al., but substantially longer than the 127 hours reported by Yagui et al. (18-19). These differences may stem from differing approaches to NIV-NAVA weaning, as evidence-based guidelines are currently lacking, with only an eminence-based guideline available (21). Additionally, Yagui et al. did not specify the criteria for defining NIV in their study, and the high standard deviation in their reported NIV duration suggest considerable variability in their cohort (19).

We observed a 22.2% treatment failure rate among infants receiving NIV-NAVA, comparable to the 20.3% reported by Yagui et al., though lower than the 30-35% failure rates documented by Kallio et al. and Lee et al. (17-19). These differences are likely due to varying definitions of treatment failure. Additionally, Lee et al. maintained a constant PEEP and a NIV-NAVA level of 1 $cmH_2O/\mu V$, while effective unloading of the infants' respiratory effort typically requires individualized titration of NAVA levels based on the patient's Edi values (9,18). Therefore, higher NAVA levels may be necessary to optimally support infants with respiratory distress and to prevent treatment failure. Shin et al. supports this theory, as they used higher levels of NIV-NAVA before reintubation, with a median level of 2.5 $cmH_2O/\mu V$, and documented a lower failure rate of 8.6% (20). In our study, the median NIV-NAVA level before reintubation was 2 $cmH_2O/\mu V$ (IQR 1.3-2).

Subgroup analysis in our study revealed a higher failure rate (45.5%) in infants born below 28 weeks of gestation, compared to those born after 28 weeks (12%). This highlights the considerable challenges encountered with the application of NIV-NAVA in extremely premature infants, likely due to a combination of pulmonary immaturity and poor respiratory drive. Nevertheless, despite these challenges, our

experience suggests that most infants in this subgroup ultimately achieve successful weaning to NIV-NAVA.

Regarding BPD, 9 (15%) infants in the overall cohort developed the condition, with the incidence rising to 29% among those treated with NIV-NAVA. However, because of the relatively low overall incidence of BPD in our cohort and the complex, multifactorial nature of the disease, no definitive conclusions can be drawn. We found no statistically significant difference in the mean LUS-score at inclusion between infants with BPD and without BPD, consistent with the findings of Woods et al, suggesting that early LUS scores may offer little beyond the established early clinical markers (22).

In terms of safety, we observed 1 case of pneumothorax and 1 case of pulmonary haemorrhage among infants receiving NIV-NAVA. To our knowledge, this is the first reported case of pulmonary haemorrhage in an infant receiving NIV-NAVA. However, as both conditions are known complications of RDS, the primary indication for initiating NIV in these infants, it is difficult to establish a definitive causal link with NIV-NAVA. Gastrointestinal symptoms related to gastrointestinal air associated with NIV-NAVA were not reported due to the lack of clear definitions for these complications, which is a recognized limitation of our study.

Another important limitation of our study arises from its observational nature, which inherently restricts the ability to draw causal relationships. The study is subject to potential confounding factors and selection bias, particularly since not all eligible infants were included. Additionally, the single- centre design limits the generalizability of our findings, and the small sample size in certain subgroups make it difficult to draw definitive conclusions about specific outcomes, such as BPD or treatment failure rates.

Despite these limitations, our study demonstrates that NIV-NAVA is a feasible and safe mode of respiratory support for preterm infants, even in those with significant with significant respiratory challenges. Its use across a wide range of GA, alongside other modes of NIV, highlights its adaptability in clinical practice.

Future research should aim to deepen our understanding of the physiological effects of NIV-NAVA, as this could be useful to develop evidence-based guidelines for its use and weaning. Larger studies with extended follow-up are necessary to assess long-term outcomes, including BPD and other adverse events. Multi-centre trials are necessary to enhance the external validity of our findings, and randomised controlled trials comparing NIV-NAVA with other NIV modes, are crucial to definitively establish its efficacy and safety.

Conclusion

Our study is one of the first prospective observational studies investigating NIV-NAVA in relation to more commonly used forms of NIV in preterm infants from birth to discharge from the NICU. Our findings illustrate the feasibility and safety of NIV-NAVA across various ranges of GA and alongside other modes of NIV, despite higher failure rates observed in extremely preterm infants. The incidence of BPD among infants receiving NIV-NAVA was 29%. Further research is needed to achieve a more comprehensive understanding of NIV-NAVA's efficacy and safety profile. It is also crucial to gain a deeper understanding of its psychological effects for optimizing its application and to obtain a clearer view of long-term outcomes.

None of the investigators had any conflicts of interest.

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