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Implementation of neurally adjusted ventilatory assist and high flow nasal cannula in very preterm infants in a tertiary level NICU

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Abstract

Preterm infants treated with invasive ventilation are often affected by bronchopulmonary dysplasia, brain structure alterations, and later neurodevelopmental impairment. We studied the implementation of neurally adjusted ventilatory assist (NAVA) and high flow nasal cannula (HFNC) in a level III neonatal unit, and its effects on pulmonary and central nervous system outcomes. This retrospective cohort study included 193 surviving infants born below 32 weeks of gestation in preimplementation (2007–2008) and postimplementation (2016–2017) periods in a single study center in Finland. The proportion of infants requiring invasive ventilation decreased from 67% in the pre- to 48% in the postimplementation period ($p = 0.009$). Among infants treated with invasive ventilation, 68% were treated with NAVA after its implementation. At the same time, the duration of invasive ventilation of infants born at or below 28 weeks increased threefold compared with the preimplementation period ($p = 0.042$). The postimplementation period was characterized by a gradual replacement of nasal continuous positive airway pressure (nCPAP) with HFNC, earlier discontinuation of nCPAP, but a longer duration of positive pressure support. The proportion of normal magnetic resonance imaging (MRI) findings at term corrected age increased from 62% to 84% ($p = 0.018$). Cognitive outcome improved by one standard score between the study periods ($p = 0.019$). NAVA was used as the primary mode of ventilation in the postimplementation period. During this period, invasive ventilation time was significantly prolonged. HFNC led to a decrease in the use of nCPAP. The change in the respiratory support might have contributed to the improvement in brain MRI findings and cognitive outcomes.

Abbreviations: Bayley-III, Bayley Scales of Infant Development—Third Edition; BPD, bronchopulmonary dysplasia; HFNC, high flow nasal cannula; HFO, high-frequency oscillation; IVH, Intraventricular hemorrhage; MRI, magnetic resonance imaging; NAVA, neurally adjusted ventilatory assist; nCPAP, nasal continuous positive airway pressure; NICU, neonatal intensive care unit; NIV-NAVA, non-invasive neurally adjusted ventilatory assist; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity; SIMV + PS, synchronized intermittent mandatory ventilation + pressure support.

A part of the data has been presented as a poster presentation during the 8th Congress of the European Academy of Paediatric Societies (EAPS2020).

KEYWORDS
HFNC, invasive ventilation, NAVA, noninvasive ventilation, preterm infant

1 | INTRODUCTION

Endotracheal intubation followed by mechanical ventilation is a life-saving therapy for preterm infants with acute respiratory failure, although it comes at a price. Conventional ventilation is a known risk factor for the development of bronchopulmonary dysplasia,[1,2] brain structure alterations, and later neurodevelopmental impairment.[3–7] The emergence of neurally adjusted ventilatory assist (NAVA) has offered a promise of gentler respiratory support.[8] NAVA uses the signal of the diaphragm's electrical activity to trigger inflation and to fine-tune the pressure proportionally to the infant's own breathing effort.[9] The beneficial effects of this mode are related to better patient–ventilator interaction leading to improved synchrony, lower peak inspiratory pressure, and a lower fraction of inspired oxygen needed to achieve ventilatory targets.[10,11] Despite this promising profile, the role of NAVA in neonatal ventilatory support has not been established.

Noninvasive methods of respiratory support are widely used in neonatal intensive care units (NICUs). Nasal continuous positive airway pressure (nCPAP) is used both as initial and postextubation respiratory support in preterm infants.[12,13] The use of a high flow nasal cannula (HFNC) has been proven to be less effective than nCPAP as primary support in preterm infants; however, it is considered clinically equal as postextubation support.[14–16] HFNC has been commonly used as a step-down mode from nCPAP, but studies investigating the efficacy of this method are inconclusive.[17–19] In addition to nCPAP and HFNC, neurally adjusted methods can also offer support in a noninvasive mode.[20] Infants extubated to NIV-NAVA remain extubated longer and have lower peak inspiratory pressures compared with nasal intermittent positive pressure ventilation.[21]

Over 10 years, the care practices in our NICUs have evolved towards solutions that support noninvasive and gentle ventilation. This retrospective cohort study investigates the implementation of NAVA and HFNC in a tertiary NICU and its effects on the pulmonary and central nervous system outcomes.

2 | MATERIALS AND METHODS

This retrospective cohort study was conducted in a level III NICU of Turku University Hospital, Finland. The unit implemented NAVA respiratory support in 2009, and HFNC in 2011. The study population included infants born below 32 weeks of gestation before (2007–2008) and after (2016–2017) the implementation of these respiratory support methods.

A predefined set of patient characteristics, duration of ventilatory support, and outcome measures was collected. Modes of invasive ventilation included NAVA, SIMV + PS (synchronized intermittent mandatory ventilation + pressure support), and HFO (high-frequency oscillation). After its implementation, NAVA was used as the method of choice of invasive ventilation for all neonates who were expected to be ventilated for longer than 24 h. This policy to exclude infants with very short ventilation periods from the NAVA treatment was based on the economic burden created by the cost of Edi catheters. HFO ventilation was used exclusively as a rescue therapy throughout both study periods. The duration of invasive ventilation was collected in half-hour intervals. A period of invasive ventilation was defined as the time between intubation and extubation. Two invasive ventilation periods were considered separate if the period of extubation between them was more than 6 h. Periods of invasive ventilation associated with surgical procedures performed outside of the invasive ventilation period were excluded and did not contribute to the total duration of the invasive ventilation. Modes of noninvasive ventilatory support included NIV-NAVA (noninvasive NAVA), nCPAP, HFNC, and low-flow supplemental oxygen. NIV-NAVA was offered mostly to patients extubated from NAVA with already placed Edi catheter. Weaning from nCPAP to HFNC and no support was a shared decision, based on clinical evaluation. When infants reached nCPAP of 4 cm H_2O, they started to alternate between nCPAP and HFNC of 6 L/min. Periods of noninvasive respiratory support were reported as the postmenstrual age when each mode of support was used for the last time. We defined the end of any positive-pressure support as the last day when either invasive ventilation, NIV-NAVA, nCPAP, or HFNC 4–6 L/min was used. Bronchopulmonary dysplasia (BPD) was defined as a need for supplemental oxygen at 36 weeks of postmenstrual age.

Early nCPAP was used in both study periods, for all spontaneously breathing infants or infants starting to breathe spontaneously after brief positive-pressure support. Surfactant was administered following the same protocol in both study periods (infants requiring $FiO_2\% > 0.4$, pH < 7.25, or apnea requiring positive pressure ventilation).

The Servo-i ventilators (Getinge) were used to provide SIMV + PS support until updated with NAVA and NIV-NAVA (noninvasive NAVA) modules in 2009. HFO support was delivered by a Stephanie ventilator (Fritz Stephan GMBH) until 2012 when it was replaced by a Leoni+ ventilator (Löwenstein Medical GmbH & Co. KG). Nasal CPAP was delivered with Infant Flow devices (Vyaire Medical) until 2015 when they were replaced with the Fabian device (Acutronic). NIV-NAVA ventilatory support was started in 2010 and HFNC in 2011. HFNC support was first delivered as a humidified gas mixture, and since 2015 with the Fabian device. Servo-n ventilators (Getinge) were purchased in 2017.

A magnetic resonance imaging (MRI) examination was performed as a part of the routine examination at term corrected age. The MRI equipment was a 1.5 Tesla Siemens Avanto or Aera (Siemens Medical Systems). The brain MRI results were categorized as normal findings, minor or major pathologies (Table 1).[22]

At 2 years of corrected age, children were routinely assessed by psychologists as a part of their clinical follow-up, using the Bayley Scales of Infant Development—Third Edition (Bayley-III).[23] The Bayley-III generates scores for three composite indices (Cognitive, Language,

Motor) and five subtests (Cognitive, Expressive Communication, Receptive Communication, Fine Motor, Gross Motor). In this study, we focused on the cognitive scale, which estimates general cognitive functioning based on nonverbal activities involving memory, problem-solving, and manipulation. Age-standardized scores were calculated by using test norms (mean = 10; SD = 3).

Changes in the care practices throughout the studied periods are described in Figure 1. They include the introduction of the "Close collaboration with parents training" program (2009),[24] the replacement of theophylline with caffeine citrate (2010), and the transfer of the NICU to a new location, featuring 11 single-family rooms (2014) (Figure 1).

Due to the inability to collect complete respiratory support data, we excluded infants who had died during their initial hospital stay or were transferred during their respiratory support to centers outside the hospital district. One infant from the study cohort was tracheostomized due to tracheogranuloma and excluded due to a nonpulmonary reason for protracted ventilation.

The primary outcomes were the proportion of NAVA ventilation of the total duration of invasive ventilation and the duration of respiratory support in infants born below 32 weeks of gestation. The secondary objective was to compare the clinical pulmonary and central nervous system outcomes in infants born before and after the NAVA/HFNC implementation.

2.1 | Statistical analysis

For the continuous variables, data are presented as median (IQR) or mean (±SD) depending on the distribution, and for categorical variables as *n* (%). For continuous measurement data, normal distribution variables were analyzed by *t* test, and non-normal distribution variables by the Mann–Whitney *U* test. Categorical variables were tested with Fisher's exact test or χ^2 test. Statistical analyses were performed in SPSS Statistics v. 27. We considered a *p* value of <0.05 to be statistically significant.

3 | RESULTS

3.1 | Patient characteristics

During the studied periods, 216 infants born below 32 weeks of gestation were admitted to the unit. Seven infants were excluded because of a transfer outside of the hospital district. Of the remaining 209 infants, 96 were born during the preimplementation period (2007–2008) and 113 in the postimplementation period (2016–2017).

Infants in the preimplementation period had a mean birth weight of 1208 g (min, 420 g; max, 2180 g) and median gestational age of 29 weeks (min, $24^{1/7}$ weeks; max, $31^{6/7}$ weeks), and in the postimplementation period 1230 g (min, 400 g; max, 3060 g) and $29^{4/7}$ weeks (min, 23 weeks; max $31^{6/7}$ weeks). The frequency of Cesarean sections in the preimplementation period was lower than in the postimplementation period (51% vs. 74%, $p = 0.001$). There were more multiple pregnancies in the preimplementation period (42% vs. 27%, $p = 0.027$). Umbilical cord blood pH differed between the study periods, although both median values were clinically within the normal range. The proportion of infants small for gestational age, male-to-female ratio, administration of maternal steroids, and Apgar scores at 1 and 5 min did not differ between the studied periods (Table 2).

In the subgroup of infants born at or below 28 weeks of gestation, 34 infants were born in the preimplementation period and 31 in the postimplementation period. They had similar birth weights and median gestational age at birth. The decrease in the proportion of multiple pregnancies was similar in this subpopulation (Table 2).

TABLE 1 Brain magnetic resonance imaging findings[22]

Normal findings	Normal brain anatomy (cortex, basal ganglia and thalami, posterior limb of the internal capsule, white matter, germinal matrix, corpus callosum, and posterior fossa structures)
	A width of extracerebral space <5 mm, ventricular/brain ratio <0.35
	No ventriculitis
Minor pathologies	Consequences of intraventricular hemorrhages grades 1 and 2
	Caudothalamic cysts
	A width of the extracerebral space of 5 mm
	A ventricular/brain ratio of 0.35
Major pathologies	Consequences of intraventricular hemorrhages grades 3 and 4
	Injury in the cortex, basal ganglia, thalamus, or internal capsule, with an injury of the corpus callosum, cerebellar injury, white matter injury
	Increased width of extracerebral space >5 mm
	A ventricular/brain >0.35, ventriculitis
	Other major brain pathology (infarcts)

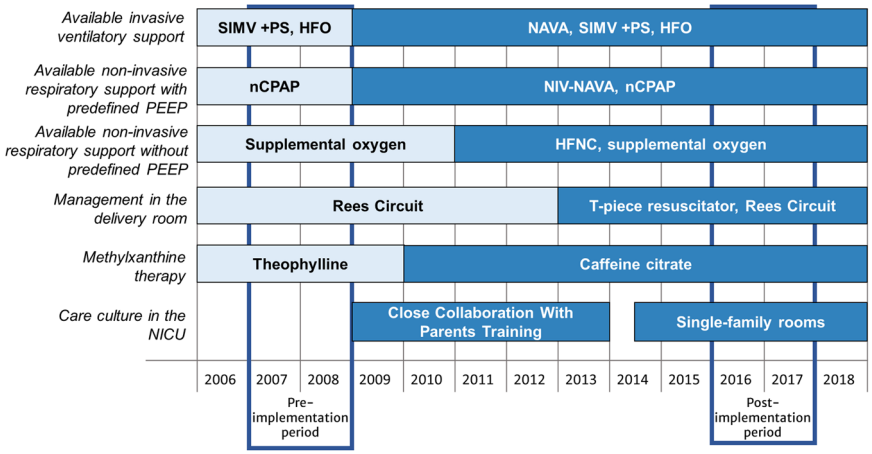

FIGURE 1 Changes in respiratory care practices. HFO, high-frequency oscillation; NAVA, neurally adjusted ventilatory assist; PEEP, positive end-expiratory pressure; SIMV + PS, synchronized intermittent mandatory ventilation + pressure support

Seven infants died during their initial hospitalization in the preimplementation period, eight in the postimplementation period. One infant was excluded from further analysis due to nonpulmonary reasons of protracted ventilation.

3.2 | Delivery room management

In the whole cohort, the proportion of infants supported with positive pressure ventilation, intubated, treated with surfactant, or who received chest compressions in the delivery room did not differ across the studied periods (Table 2). There was an increase in the use of nCPAP in the delivery room: in the preimplementation period, 78% of infants received nCPAP, compared with 89% in the postimplementation period. The subpopulation of infants born at or below 28 weeks of gestation received similar support in the delivery room during both periods (Table 2).

3.3 | Ventilatory support during the hospital stay

Ventilatory support data are presented only for the surviving infants.

The proportion of infants treated with invasive ventilation decreased significantly between the studied periods: from 67% in the preimplementation period to 48% in the postimplementation period ($p = 0.009$). During the preimplementation period, 75% of hours of invasive ventilation were delivered using SIMV + PS; whereas, during the postimplementation period, 54% of hours were delivered using NAVA (Figure 2). Among infants requiring invasive ventilation, 68% were treated with NAVA in the postimplementation period (data not shown). The median duration of invasive ventilation during the preimplementation period was 23.5 h, compared with zero-hours in the postimplementation period (data not shown). We observed a similar change of the preferred mode of invasive ventilation also in infants born at or below 28 weeks of gestation (Figure 2).

In the subpopulation of infants born at or below 28 weeks of gestation, the duration of invasive ventilation increased more than threefold between the studied periods (Table 3). The duration of the first episode of invasive ventilation increased from 1.6 to 8.5 days ($p = 0.045$). Most infants in both periods had more than one episode of invasive ventilation. The majority of infants in the postimplementation period were treated with both SIMV + PS and NAVA modes. The duration of SIMV + PS ventilation decreased from 5 to 2.3 days, but the difference did not reach statistical significance. Seventeen out of 22 infants using NAVA were switched to NAVA mode during their first day of life. The median duration of NAVA ventilation was 17.5 days. There was a trend towards a decrease in the median duration of HFO ventilation between the studied periods.

In the whole population, HFNC was used until the median postmenstrual age of 34 weeks ($32^{5/7}$–$35^{5/7}$weeks) during the postimplementation period. The implementation of HFNC led to the shortening of nCPAP treatment but simultaneously increased the total time of any positive pressure support (Table 4). Nine infants were treated with NIV-NAVA during the postimplementation period.

There was no difference in the postmenstrual age at the end of nCPAP treatment between the studied periods in the subpopulation of infants born at or below 28 weeks of gestation. During the postimplementation period, HFNC was used as the last mode of respiratory support in 96% of the infants. Their HFNC treatment ended at a median of $35^{4/7}$ weeks of postmenstrual age. The total length of positive pressure respiratory support was longer during the postimplementation period than during the preimplementation period ($33^{2/7}$ vs. $35^{6/7}$ weeks of postmenstrual age, $p = 0.001$).

3.4 | Respiratory and nonrespiratory outcomes

There was no difference in the incidence of BPD nor the composite outcome of BPD or death between the studied periods. Six out of 89 infants in the preimplementation and 13 out of 104 in the postimplementation period required supplemental oxygen at 36 weeks of postmenstrual age. In the subpopulation of infants born at or below 28 weeks, it was two out of 28 and five out of 24 infants, respectively (Table 4). The length of stay remained unchanged between the study periods.

TABLE 2 Characteristics and management in the delivery room of infants born below 32 weeks of gestation

	Born <32 weeks of GA			Born ≤28 weeks of GA		
	Preimplementation (*n* = 96)	Postimplementation (*n* = 113)	*p*	Preimplementation (*n* = 34)	Postimplementation (*n* = 31)	*p*
Birthweight[a], g	1208 (375)	1230 (414)	0.694	852 (224)	816 (256)	0.60
Gestational age[b], weeks	29 (27.3–30.8)	29.4 (27.9–30.9)	0.243	26.9 (24.8–27.4)	27 (25.6–27.6)	0.532
SGA, *n* (%)	20 (21%)	26 (23%)	0.74	4 (12%)	8 (26%)	0.2
Male, *n* (%)	54 (56%)	51 (45%)	0.127	18 (53%)	18 (58%)	0.8
Multiple pregnancy, *n* (%)	40 (42%)	30 (27%)	0.027	11 (32%)	0 (0%)	<0.001
Maternal steroids, *n* (%)			0.226			1
One dose	26 (27%)	25 (22%)		8 (24%)	8 (26%)	
Full course	64 (67%)	86 (76%)		23 (70%)	21 (68%)	
C-section, *n* (%)	48 (51%)	83 (74%)	0.001	17 (50%)	20 (65%)	0.317
APGAR 1 min <5, *n* (%)	30 (32%)	26 (23%)	0.2	18 (53%)	14 (45%)	0.622
APGAR 5 min <5, *n* (%)	14 (15%)	12 (11%)	0.407	12 (35%)	8 (27%)	0.591
Umbilical cord pH[b]	7.34 (7.3–7.37)	7.3 (7.24–7.36)	0.02	7.34 (7.29–7.37)	7.36 (7.27–7.4)	0.448
Positive pressure ventilation in DR, *n* (%)	52 (54%)	60 (53%)	0.89	25 (74%)	23 (74%)	1
nCPAP in DR, *n* (%)	75 (78%)	101 (89%)	0.036	21 (62%)	21 (68%)	0.796
Intubation in DR, *n* (%)	19 (20%)	16 (14%)	0.353	15 (44%)	11 (36%)	0.613
Surfactant in DR, *n* (%)	10 (10%)	13 (12%)	0.829	9 (27%)	10 (32%)	0.785
Chest compressions in DR, *n* (%)	3 (3%)	5 (4%)	0.729	3 (9%)	3 (10%)	1

Abbreviations: DR, delivery room; IQR, interquartile range; SGA, small for gestational age.

[a]Data presented as mean (±SD).

[b]Data presented as median (IQR).

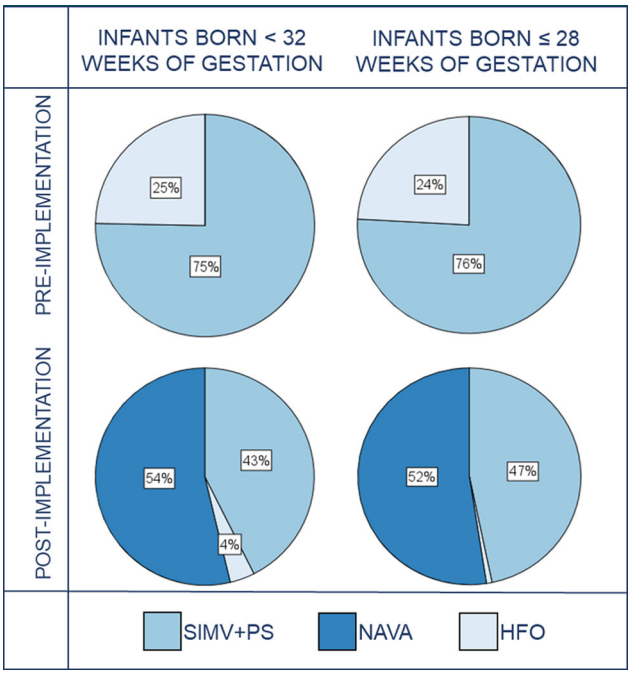

FIGURE 2 Distribution of various invasive ventilatory support modes in infants born below 32 weeks of gestation and in the subpopulation of infants born at or below 28 weeks of gestation. HFO, High-frequency oscillation; NAVA, neurally adjusted ventilatory assist; SIMV + PS, synchronized intermittent mandatory ventilation + pressure support

The brain MRI imaging was performed for 82 infants during the preimplementation period and 95 infants during the postimplementation period, representing 92% and 91% of the infants, respectively. The MRI results showed that the proportion of infants with normal findings increased from 64% to 82% ($p = 0.018$). A similar trend was found in infants born at or below 28 weeks. The occurrence of severe IVH, PVL, or severe ROP did not differ between the studied periods (Table 4).

In the population of infants born <32 weeks of gestation, the cognitive outcome (Bayley-III) at 2 years of corrected age was one standard score higher in children in the postimplementation period compared with children in the preimplementation period ($p = 0.019$). For the subgroup of infants born at or below 28 weeks, the cognitive outcome was also one standard score higher in the postimplementation period, but the difference did not reach statistical significance ($p = 0.373$).

4 | DISCUSSION

This study showed that NAVA and HFNC could be successfully implemented in a tertiary NICU. To our knowledge, this is the first study reporting implementation of NAVA as the primary mode of support for preterm infants: more than 90% of infants born at or below 28 weeks of gestation were supported with NAVA in our cohort. Ninety-nine percent of infants born below 32 weeks of gestation in the postimplementation period were supported with HFNC. Implementation of HFNC replaced a significant proportion of nCPAP days, but it increased the time of any positive pressure support.

To date, there is only one randomized controlled trial comparing NAVA and conventional ventilation in preterm infants, showing that NAVA is safe and feasible in supporting infants born at 28 weeks gestation or later.[25] In addition, several cross-over comparisons describe the short-term physiological benefits of NAVA in a population comparable with ours.[26–28] However, to our knowledge, this is the first report describing the systematic use of NAVA as a primary mode of ventilation in preterm infants. This study showed a clear change in the preferred mode of invasive ventilation, from conventional ventilation to NAVA. After implementing NAVA, more than 50% of invasive ventilation hours were provided in this mode. Those hours which were not provided with NAVA included short ventilator therapies that deliberately were provided with SIMV + PS, and NAVA failures, including patient's clinical deterioration.[29] Despite the concerns regarding the maturity of neural respiratory control in preterm infants,[9,30] our study clearly showed that even the most preterm infants can be supported with NAVA. It was used for 92% of infants born at or below 28 weeks of gestation, with a median of 75% of their total invasive ventilation time spent in NAVA. Together with recent data published by our group, this study supports the suggestion that preterm infants exhibit functional maturity of respiratory control and have sufficient feedback mechanisms, allowing NAVA ventilation.[29,31] Most infants were switched to NAVA already on their first day of life; however, the median number of NAVA ventilation episodes was three, meaning that most of the infants also needed other invasive respiratory modes.

The time following the implementation of NAVA was characterized by fewer intubations but longer periods of ventilation for those intubated. The prolonged ventilation might be explained by the reluctance to extubate when the infant seemed to be comfortable with the provided support, and especially when the success of extubation was considered uncertain. Nevertheless, this protracted invasive ventilation raises concerns regarding the long-term outcomes of exposed infants. According to previous reports, prolonged ventilation times with conventional ventilation modes are associated with worse developmental outcomes.[5,7,32] However, those studies used flow or pressure-triggered ventilation modes, possibly leading to insufficient patient–ventilator synchrony, which may result in sleep disruption and increased exposure to pain medication or sedation. Neonates treated with conventional ventilation and/or high-frequency ventilation for a prolonged time were shown to have lower pons and medulla volumes compared with infants ventilated for shorter periods.[3] This is in contrast to a recently published study from our center, which showed no difference between the regional brain volumes of extremely preterm infants before and after implementation of NAVA.[33] Together these results suggest that NAVA-associated prolongation of invasive ventilation did not negatively affect the central nervous system outcomes. On the contrary, we observed a considerable increase in the proportion of

TABLE 3 Invasive ventilation in surviving infants born at or below 28 weeks of gestation

	Preimplementation (*n* = 28)	Postimplementation (*n* = 24)	*p*
The total duration of invasive ventilation			
Age at start[a], h	0.5 (0.5–0.5)	0.5 (0–2)	0.091
Duration[a], days	5.9 (2–16.7)	19.9 (6.5–40.9)	0.042
Number of intubations[a]	2 (1–2)	2 (1–2)	1
Duration of the 1st episode[a], days	1.6 (0.8–9.7)	8.5 (1.4–25.9)	0.045
SIMV + PS			
n (%)	28 (100)	23 (96)	0.462
Age at start[a], h	0.5 (0.5–0.5)	0.5 (0–2)	0.16
Duration[a], days	5 (2–13.6)	2.3 (0.6–9.8)	0.098
HFO			
n (%)	12 (43)	4 (17)	0.07
Age at start[a], h	46 (3–242.5)	253 (69–796.5)	0.17
Duration[a], days	4.6 (2.8–7.7)	1.8 (0.7–3)	0.078
NAVA			
n (%)	-	22 (92)	
Age at start[a], h	-	11 (3.5–27.5)	
Duration[a], days		17.5 (5-39.6)	

Abbreviations: HFO, high-frequency oscillation; IQR, interquartile range; NAVA, neurally adjusted ventilatory assist; SIMV + PS, synchronized intermittent mandatory ventilation + pressure support.

[a]Data presented as median (IQR).

normal brain MRI findings between the studied periods. This finding is further supported by improvement in cognitive outcome assessed using the Bayley-III at 2 years of corrected age.

Invasive ventilation is also a risk factor for developing bronchopulmonary dysplasia, but practices aiming to avoid endotracheal intubation bring only modest benefit in preventing this condition.[34,35] Up to 65% of spontaneously breathing preterm infants fail noninvasive ventilation strategies as the primary mode of support and have to be intubated.[36] For these infants especially, neurally adjusted modes could be gentler for the lungs. Although studies suggest that the cumulative duration of ventilation is associated with an increased risk of BPD,[5] our rates remained stable between the study periods despite the longer invasive ventilation times. This might be due to better synchrony, lower peak inspiratory pressure, and a lower fraction of inspired oxygen, possibly protecting the lung during NAVA ventilation.[26,37] Some infants were discharged with the home oxygen therapy during the postimplementation period which is likely to be a result of earlier discharge rather than an increase in severe BPD.

HFNC has rapidly gained popularity in our unit. It was preferred over nCPAP by nurses and parents due to its easy setup, the observed benefits on infant comfort, and a lowering of the threshold for parents to participate in infant care. This observation is in agreement with previous studies concluding that parents and nurses preferred HFNC over nCPAP although there was no measurable difference in infants' comfort.[38,39] However, studies suggest that the introduction of HFNC reduces the duration of nCPAP support, but increases the total duration of positive pressure support.[40,41] Our finding was consistent with the previous studies: we found a decrease of 8.5 days in the nCPAP days and an increase of 10.5 days in any positive pressure respiratory support. Similarly to other studies, we used HFNC mostly as a weaning mode from nCPAP. An earlier study reported a trend toward higher BPD and ROP rates after HFNC introduction,[41] but our study did not confirm these findings. Currently, there are no recommendations on how or when to discontinue HFNC treatment in preterm infants.[42] Typically, the decision to discontinue HFNC is based on multiple factors including the need for supplemental oxygen, the work of breathing, apnea, and the ability to (breast)feed. The effects of different strategies should be studied from all these perspectives. Additionally, we have included parents in the decision-making which may have affected the duration of support.

NIV-NAVA was used only in nine patients in the postimplementation period. This mode of noninvasive ventilation was offered primarily to patients who already had an Edi catheter in place to avoid additional costs of the Edi catheter.

Our study had good coverage for the whole population of very preterm infants of the unit. Although the study was retrospective, we were able to collect detailed data with a 30-min accuracy for the length of invasive ventilation and to reliably determine the end of respiratory support as the data were also collected from the step-down units. The brain MRI data were available for almost all the infants as the examination was performed routinely at term corrected age. We also acknowledge the

TABLE 4 Pulmonary and central nervous system outcomes of surviving infants

	Born <32weeks GA			Born ≤28weeks GA		
	Preimplementation (*n* = 89)	Postimplementation (*n* = 104)	*p*	Preimplementation (*n* = 28)	Postimplementation (*n* = 24)	*p*
PMA at the end of nCPAP,[a] weeks	32.6 (31.7–34.4)	31.4 (30.6–32)	<0.001	33.1 (31.6–34.8)	32.6 (30.1–34)	0.278
PMA at the end of any PPS,[a]weeks	32.6 (31.7–34.7)	34.1 (32.7–35.7)	<.001	33.3 (31.5–35.3)	35.8 (34.2–38.7)	0.001
Supplemental oxygen at Week 36, *n* (%)	6 (7)	13 (12)	0.228	2 (7)	5 (21)	0.227
Supplemental oxygen at Week 36 or death,[b], *n*(%)	13 (14%)	21 (19%)	0.397	8 (24%)	11 (36%)	0.226
Invasive ventilation at Week 36, *n* (%)	1 (1)	3 (3)	0.626	1 (4)	2 (8)	0.59
nCPAP at Week 36, *n* (%)	8 (9)	4 (4)	0.231	4 (14)	3 (12)	1
HFNC at Week 36, *n* (%)	—	23 (22)	—	—	10 (41)	-
Dexamethasone, *n* (%)	4 (4)	2 (2)	0.417	3 (11)	1 (4)	0.615
Home oxygen therapy, *n* (%)	1 (1)	6 (6)	0.126	0	3 (12)	0.092
Length of stay,[a] days	57 (42.5–80)	57.5 (44–78)	0.970	86 (71–108)	80 (66.5–104)	0.4
IVH severe, *n* (%)	5 (6)	4 (4)	0.735	5 (18)	3 (12)	0.711
PVL, *n* (%)	0	4 (4)	0.125	0	3 (12)	0.092
ROP requiring laser treatment, *n* (%)	3 (4)	4 (4)	1	3 (11)	3 (12)	1
Brain MRI, *n* (%)			0.018			0.544
Normal findings	52 (64)	78 (82)		16 (60)	17 (74)	
Minor pathologies	15 (18)	9 (10)		5 (18)	3 (13)	
Major pathologies	15 (18)	8 (8)		6 (22)	3 (13)	
Standard cognitive score at 2 years of corrected age[a]	10 (8–12)	11 (9–12)	0.019	10 (7–12)	11 (8–12.5)	0.373

Abbreviations: GA; gestational age; HFNC, High flow nasal cannula; IQR, interquartile range; IVH severe, IVH grade III and IV; MRI, magnetic resonance imaging; nCPAP, Nasal continuous positive airway pressure; PMA, postmenstrual age; PPS, positive pressure support; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

[a]Data presented as median (IQR).

[b]Includes also deceased infants.

limitations of our study. First, it was a retrospective, single-center study. Second, we are aware of the changes in the care practices between the studied periods. In 2009–2012, the unit carried out an educational training program for the staff to learn shared decision-making with parents. In 2014, the unit moved to a new location with single-family rooms, offering parents the possibility to be present in the unit throughout the 24-h day (Figure 1). Another possible limitation is the moderate attrition rate regarding the cognitive assessment as a part of routine clinical follow-up at 2 years of corrected age. However, the follow-up rate was similar in both groups (65%). We are also aware of other intangible changes in neonatal medicine which could have contributed to the overall improvement in the neurodevelopment of preterm infants. Considering these limitations, we are unable to establish the causal relationship between the introduction of these new respiratory support modes and clinical outcomes.

This retrospective study showed that NAVA ventilation can be used as the primary mode of ventilation even in the most preterm infants. NAVA-associated prolongation of invasive ventilation time did not have a negative impact on brain MRI results at term corrected age nor on standard cognitive scores at 2 years of corrected age. However, randomized controlled studies with neurodevelopmental outcomes are needed to establish the role of NAVA ventilation among preterm infants. Implementation of HFNC led to the shortening of nCPAP treatment, offering a comfortable continuation of less invasive respiratory support.

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CONFLICTS OF INTEREST

Drs. Liisa Lehtonen and Hanna Soukka have given academic lectures about neurally adjusted ventilatory assist in scientific conferences with support from the Getinge and Fukuda Denshi companies. Dr. Katarzyna Piątek has received financial support from the Getinge Company through Turku University Hospital for her research time in another project. Getinge Company had no role in the study design, data collection, analysis, interpretation of data, writing of the manuscript, nor in the decision to submit this manuscript to *Pediatric Pulmonology*.

AUTHOR CONTRIBUTIONS

Katarzyna Piatek: Conceptualization (equal); data curation (lead); formal analysis (lead); funding acquisition (equal); investigation (equal); methodology (equal); project administration (equal); software (equal); visualization (equal); writing—original draft (lead); writing—review and editing (equal). **Liisa Lehtonen**: Conceptualization (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); supervision (equal); validation (equal); writing—review and editing (equal). **Vilhelmiina Parikka**: Conceptualization (lead); data curation (equal); formal analysis (equal); funding acquisition (equal); investigation (equal); methodology (equal); supervision (equal); writing—review and editing (equal). **Sirkku Setänen**: Conceptualization (supporting); data curation (equal); formal analysis (equal); validation (equal), writing—review and editing (equal). **Hanna Soukka**: Conceptualization (equal); data curation (supporting); formal analysis (equal); funding acquisition (equal); methodology (equal); supervision (lead); validation (equal); writing—original draft (equal); writing—review and editing (equal).

DATA AVAILABILITY STATEMENT

Data are available upon a considerable request.

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REFERENCES

1. Beltempo M, Isayama T, Vento M, et al. Respiratory management of extremely preterm infants: an international survey. *Neonatology*. 2018;114(1):28-36. doi:10.1159/000487987
2. Abman SH, Collaco JM, Shepherd EG, et al. Interdisciplinary care of children with severe bronchopulmonary dysplasia. *J Pediatr*. 2017;181(12):12-28.e1. doi:10.1016/j.jpeds.2016.10.082
3. Guillot M, Guo T, Ufkes S, et al. Mechanical ventilation duration, brainstem development, and neurodevelopment in children born preterm: a prospective cohort study. *J Pediatr*. 2020;226(87):87-95.e3. doi:10.1016/j.jpeds.2020.05.039
4. Vliegenthart RJS, Van Kaam AH, Aarnoudse-Moens CSH, Van Wassenaer AG, Onland W. Duration of mechanical ventilation and neurodevelopment in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2019;104(6):F631-F635. doi:10.1136/archdischild-2018-315993
5. Bin Choi Y, Lee J, Park J, Jun YH. Impact of prolonged mechanical ventilation in very low birth weight infants: results from a National Cohort Study. *J Pediatr*. 2018;194(34):34-39.e3. doi:10.1016/j.jpeds.2017.10.042
6. Vliegenthart RJS, Onland W, Van Wassenaer-Leemhuis AG, De Jaegere APM, Aarnoudse-Moens CSH, Van Kaam AH. Restricted ventilation associated with reduced neurodevelopmental impairment in preterm infants. *Neonatology*. 2017;112(2):172-179. doi:10.1159/000471841
7. Walsh MC, Morris BH, Wrage LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr*. 2005;146(6):798-804. doi:10.1016/j.jpeds.2005.01.047
8. Arca MJ, Uhing M, Wakeham M. Current concepts in acute respiratory support for neonates and children. *Semin Pediatr Surg*. 2015;24(1):2-7. doi:10.1053/j.sempedsurg.2014.11.001
9. Claure N, Keszler M, Bancalari E. *Chapter 16—Patient–Ventilator Interaction*. 3rd ed. Elsevier Inc.; 2019. doi:10.1016/B978-0-323-54605-8.00016-7

10. Stein H, Firestone K. Application of neurally adjusted ventilatory assist in neonates. *Semin Fetal Neonatal Med*. 2014;19(1):60-69. doi:10.1016/j.siny.2013.09.005
11. Beck J, Reilly M, Grasselli G, et al. Patient–ventilator interaction during neurally adjusted ventilatory assist in low birth weight infants. *Pediatr Res*. 2009;65(6):663-668. doi:10.1203/PDR.0b013e31819e72ab
12. Chen CY, Chou AK, Chen YL, Chou HC, Tsao PN, Hsieh WS. Quality improvement of nasal continuous positive airway pressure therapy in neonatal intensive care unit. *Pediatr. Neonatol*. 2017;58(3):229-235. doi:10.1016/j.pedneo.2016.04.005
13. Shalshin A. Nasal CPAP or intubation at birth for preterm infants. *Thorax*. 2008;63(7):577. doi:10.1136/thx.2008.100925
14. Roberts CT, Owen LS, Manley BJ, et al. Nasal high-flow therapy for primary respiratory support in preterm infants. *N Engl J Med*. 2016;375(12):1142-1151. doi:10.1056/NEJMoa1603694
15. Murki S, Singh J, Khant C, et al. High-flow nasal cannula versus nasal continuous positive airway pressure for primary respiratory support in preterm infants with respiratory distress: a randomized controlled trial. *Neonatology*. 2018;113(3):235-241. doi:10.1159/000484400
16. Manley BJ, Owen LS, Doyle LW, et al. High-flow nasal cannulae in very preterm infants after extubation. *N Engl J Med*. 2013;369(15):1425-1433. doi:10.1056/NEJMoa1300071
17. Manley BJ. Nasal high-flow therapy for preterm infants: review of neonatal trial data. *Clin Perinatol*. 2016;43(4):673-691. doi:10.1016/j.clp.2016.07.005
18. Abdel-Hady H, Shouman B, Aly H. Early weaning from CPAP to high flow nasal cannula in preterm infants is associated with prolonged oxygen requirement: a randomized controlled trial. *Early Hum Dev*. 2011;87(3):205-208. doi:10.1016/j.earlhumdev.2010.12.010
19. Badiee Z, Eshghi A, Mohammadizadeh M. High flow nasal cannula as a method for rapid weaning from nasal continuous positive airway pressure. *Int J Prev Med*. 2015;6:33. doi:10.4103/2008-7802.154922
20. Tabacaru CR, Moores RR, Khoury J, Rozycki HJ. NAVA—synchronized compared to nonsynchronized noninvasive ventilation for apnea, bradycardia, and desaturation events in VLBW infants. *Pediatr Pulmonol*. 2019;54(11):1742-1746. doi:10.1002/ppul.24464
21. Makker K, Cortez J, Jha K, et al. Comparison of extubation success using noninvasive positive pressure ventilation (NIPPV) versus noninvasive neurally adjusted ventilatory assist (NI-NAVA). *J Perinatol*. 2020;40(8):1202-1210. doi:10.1038/s41372-019-0578-4
22. Setänen S, Haataja L, Parkkola R, Lind A, Lehtonen L. Predictive value of neonatal brain MRI on the neurodevelopmental outcome of preterm infants by 5 years of age. *Acta Paediatr Int J Paediatr*. 2014;103(10):994. doi:10.1111/apa.12765
23. Bayley N. *Bayley Scales of Infant and Toddler Development*. Harcourt Assessment; 2006.
24. Ahlqvist-Björkroth S, Boukydis Z, Axelin AM, Lehtonen L. Close Collaboration with Parents™ intervention to improve parents' psychological well-being and child development: description of the intervention and study protocol. *Behav Brain Res*. 2017;325:303-310. doi:10.1016/j.bbr.2016.10.020
25. Kallio M, Koskela U, Peltoniemi O, et al. Neurally adjusted ventilatory assist (NAVA) in preterm newborn infants with respiratory distress syndrome—a randomized controlled trial. *Eur J Pediatr*. 2016;175(9):1175-1183. doi:10.1007/s00431-016-2758-y
26. Stein H, Alosh H, Ethington P, White DB. Prospective crossover comparison between NAVA and pressure control ventilation in premature neonates less than 1500 grams. *J Perinatol*. 2013;33(6):452-456. doi:10.1038/jp.2012.136
27. Lee J, Kim H-S, Sohn JA, et al. Randomized crossover study of neurally adjusted ventilatory assist in preterm infants. *J Pediatr*. 2012;161(5):808-813.e2. doi:10.1016/j.jpeds.2012.04.040
28. Shetty S, Hunt K, Peacock J, Ali K, Greenough A. Crossover study of assist control ventilation and neurally adjusted ventilatory assist. *Eur J Pediatr*. 2017;176(4):509-513. doi:10.1007/s00431-017-2866-3
29. Lee J, Parikka V, Lehtonen L, Soukka H. Backup ventilation during neurally adjusted ventilatory assist in preterm infants. *Pediatr Pulmonol*. 2021;56(10):3342-3348. doi:10.1002/ppul.25583
30. Nam SK, Lee J, Jun YH. Neural feedback is insufficient in preterm infants during neurally adjusted ventilatory assist. *Pediatr Pulmonol*. 2019;54(8):1277-1283. doi:10.1002/ppul.24352
31. Protain AP, Firestone KS, McNinch NL, Stein HM. Evaluating peak inspiratory pressures and tidal volume in premature neonates on NAVA ventilation. *Eur J Pediatr*. 2020;180:i-175. doi:10.1007/s00431-020-03728-y
32. Laptook AR, O'Shea TM, Shankaran S, Bhaskar B. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. *Pediatrics*. 2005;115(3):673-680. doi:10.1542/peds.2004-0667
33. Soukka H, Parkkola R, Lehtonen L. Brain growth in extremely preterm infants before and after implementing NAVA ventilation. *Acta Paediatr*. 2021;110(6):1812-1814. doi:10.1111/apa.15749
34. Fischer HS, Bührer C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics*. 2013;132(5):1351-1360. doi:10.1542/peds.2013-1880
35. Jensen EA. Prevention of bronchopulmonary dysplasia: a summary of evidence-based strategies. *Neoreviews*. 2019;20(4):e189-e201.
36. Schmölzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. *BMJ*. 2013;347:f5980. doi:10.1136/bmj.f5980
37. Firestone KS, Fisher S, Reddy S, White DB, Stein HM. Effect of changing NAVA levels on peak inspiratory pressures and electrical activity of the diaphragm in premature neonates. *J Perinatol*. 2015;35(8):612-616. doi:10.1038/jp.2015.14
38. Klingenberg C, Pettersen M, Hansen EA, et al. Patient comfort during treatment with heated humidified high flow nasal cannulae versus nasal continuous positive airway pressure: a randomised crossover trial. *Arch Dis Child—Fetal Neonatal Ed*. 2013;99(2):134-137.
39. Roberts CT, Manley BJ, Dawson JA, Davis PG. Nursing perceptions of high-flow nasal cannulae treatment for very preterm infants. *J Paediatr Child Health*. 2014;50(10):806-810. doi:10.1111/jpc.12636
40. Sasi A, Malhotra A. High flow nasal cannula for continuous positive airway pressure weaning in preterm neonates: a single-centre experience. *J Paediatr Child Health*. 2015;51(2):199-203. doi:10.1111/jpc.12693
41. Hoffman SB, Terrell N, Driscoll CH, Davis NL. Impact of high-flow nasal cannula use on neonatal respiratory support patterns and length of stay. *Respir Care*. 2016;61(10):1299-1304. doi:10.4187/respcare.04668
42. Van Delft B, Van Ginderdeuren F, Lefevere J, Van Delft C, Cools F. Weaning strategies for the withdrawal of non-invasive respiratory support applying continuous positive airway pressure in preterm infants: a systematic review and meta-analysis. *BMJ Paediatr Open*. 2020;4(1):e000858. doi:10.1136/bmjpo-2020-000858

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