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NIV-NAVA versus NCPAP immediately after birth in premature infants: A randomized controlled trial

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ABSTRACT

Objective: To evaluate whether noninvasive-neurally adjusted ventilatory assist (NIV-NAVA) decrease respiratory efforts compared to nasal continuous positive airway pressure (NCPAP) during the first hours of life.
Methods: Twenty infants born between 28^{+0} and 31^{+6} weeks were randomized to NIV-NAVA or NCPAP. Positive end-expiratory pressure was constantly kept at 6 cmH_2O for both groups and the NAVA level was 1.0 $cmH_2O/\mu V$ for NIV-NAVA group. The electrical activity of diaphragm (Edi) were recorded for the first two hours.
Results: Peak and minimum Edi decreased similarly in both groups ($P = 0.98$ and $P = 0.59$, respectively). Leakages were higher in the NIV-NAVA group than in the NCPAP group ($P < 0.001$). The neural apnea defined as a flat Edi for ≥ 5 s were less frequent in NIV-NAVA group than in NCPAP group ($P = 0.046$).
Conclusions: Immediately applied NIV-NAVA in premature infants did not reduce breathing effort, measured as peak Edi. However, NIV-NAVA decreased neural apneic episodes compared to NCPAP.

1. Introduction

Nasal continuous positive airway pressure (NCPAP) is a standard noninvasive mode to support breathing of premature infants during the transition period after birth (Sweet et al., 2019). The positive end-expiratory pressure (PEEP) provided by NCPAP promotes lung aeration by sustaining functional residual capacity and by preventing atelectasis at end expiration. Nasal intermittent positive pressure ventilation (NIPPV) can be applied over PEEP to improve and reduce the respiratory workload. NIPPV was superior to NCPAP in reducing the need for intubation especially in the sickest and more immature infants (Bancalari and Claure, 2013), but the subgroup of premature infants that most benefits from this support still needs to be identified (Lemyre et al., 2016). Among NIPPVs, synchronized NIPPVs that attempt to achieve patient-ventilator synchrony have been shown to increase its efficacy compared with unsynchronized NIPPVs or NCPAP (Chang et al., 2011; Demoule et al., 2006; Vignaux et al., 2009). However, it is challenging to ideally synchronize the weak and rapid respiratory cycle of premature infants to rapidly trigger mechanical breath, even more difficult because of leakage around the nasal interface (Moretti and Gizzi, 2021).

Noninvasive neurally adjusted ventilatory assist (NIV-NAVA) is a support mode where the electrical activity of the diaphragm (Edi) is used as the trigger to synchronize inspiratory support with breathing effort of the infant (Beck et al., 2009; Emeriaud et al., 2006). Studies showed that patient-ventilator synchrony is improved during NIV-NAVA compared to other NIPPV modes (Beck et al., 2009; Lee et al., 2015; Matlock et al., 2020). In addition, NIV-NAVA reduced diaphragm load when compared to others even in the presence of large air leaks (Lee et al., 2015; Matlock et al., 2020). NIV-NAVA also reduced the need for supplemental oxygen and decreased the length and frequency of desaturations and bradycardias compared to other NIPPV modes (Gibu et al., 2017; Tabacaru et al., 2019a). These benefits of NIV-NAVA, shown in earlier studies, make it an intriguing technique to be studied as an alternative to the standard respiratory support, NCPAP, in the initial care of very preterm infants.

There are no previous reports describing the effect of NIV-NAVA compared to NCPAP on respiratory effort immediately after birth. We chose to study very preterm infants born between 28^{+0} and 31^{+6} weeks

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of gestational age, since more than half of extremely preterm infants < 28^{+0} weeks gestation requires tracheal intubation because of profound respiratory distress and frequent apneas (Finer et al., 2010). We hypothesized that the peak and minimum Edi values would be lower during NIV-NAVA treatment, reflecting superior respiratory support from NIV-NAVA compared to NCPAP.

2. Materials and methods

This randomized controlled study was performed to compare the early application of NIV-NAVA to NCPAP immediately after birth. The study was conducted at a level III neonatal intensive care unit in Turku University Hospital, Finland, between January 2017 and July 2019 and was approved by the Ethics Committee of the Hospital District of Southwest Finland. Written informed consent was collected from parents before delivery. Some of the NCPAP data included in this study have been published in a previous article (Oda et al., 2018).

The primary outcomes were the peak and minimum Edi values during the first two hours after birth. The secondary outcomes were neural respiratory rate (nRR), peripheral oxygen saturation (SpO_2), heart rate, fraction of inspired oxygen (FiO_2), and the number of neural apneas after birth. Neural apnea was defined as a flat Edi signal for more than 5 s

2.1. Study population

Infants born between 28^{+0} and 31^{+6} weeks of gestation were eligible for the study. The exclusion criteria were significant malformations or the need for invasive ventilatory assistance during initial stabilization after birth. Study inclusion was dependent on the availability of a research team for the operation of monitoring equipment and randomization. A convenience sample of twenty infants was chosen for this study. Randomization was performed by enclosed envelopes opened immediately before birth.

2.2. Study protocol and settings

In the delivery room, all infants received early NCPAP of PEEP 6 cmH_2O and initial FiO_2 set at 0.30. A pulse oximetry sensor (Rainbow R1–20 L, Masimo Corp, Irvine, California, USA) was attached to the right wrist of the infant. During initial stabilization, an Edi catheter was inserted as soon as possible. Infants randomized to NIV-NAVA were switched to NIV-NAVA according to the protocol immediately after the Edi catheter was positioned with the following settings: PEEP 6 cmH_2O, NAVA level 1.0 $cmH_2O/\mu V$, Edi trigger 0.5 μV, apnea time 5 s, peak inspiratory pressure limit 35 cmH_2O, backup pressure above PEEP 12 cmH_2O, backup rate 40 breaths/minute, backup inspiratory time 0.4 s. Infants who were randomized to NCPAP continued on PEEP of 6 cmH_2O. All infants received ventilatory support from a Servo-n ventilator (Getinge, Solna, Sweden) through an EasyFlow interface (Stephan, Gackenbach, Germany). The settings were sustained during transport from the delivery ward to the intensive care unit. During the study period, PEEP was constantly kept at 6 cmH_2O and the NAVA level was 1.0 $cmH_2O/\mu V$. Target SpO_2 was 90–95% in both groups. The intubation criteria were $FiO_2 > 0.4$, pH < 7.25 or frequent apnea with bradycardia requiring inflated breaths. Caffeine citrate was administered according to the attending clinician's decision.

2.3. Data acquisition and measurements

Perinatal data and in-hospital clinical outcome parameters were collected from the medical records and surveillance charts. The delivered pressure, flow, FiO_2, nRR, leakage and Edi values were acquired from a Servo-n ventilator (Getinge, Gothenburg, Sweden) through an RS232 interface at a sampling rate of 100 Hz. These data were simultaneously recorded using the dedicated software ServoTracker SCI (Maquet, Solna, Sweden). Data from ServoTracker recordings were analyzed with the Servo Analysis Tool (SAT) v2.0 (Getinge, Gothenburg, Sweden) by a blinded researcher. The SAT samples all breaths independently based on the Edi, pressure and flow signals. Breaths with an Edi integral < 0.15 μVs were filtered out in the calculation. SpO_2 and heart rate were simultaneously and continuously recorded using a Radical or Radical7 pulse oximeter (Masimo Corp, Irvine, California, USA) with a 2-second averaging time and transferred to a personal computer through an RS232 serial communication port. The mean values for all of the data were calculated by averaging them for 10-minute intervals from the time of birth, except for neural apnea count which was calculated for each 5-minute interval.

2.4. Statistical analysis

Statistical analyses were performed using SPSS v27.0 (IBM, Armonk, NY, USA). Categorical variables were analyzed using $\chi 2$ and Fisher's exact test, as appropriate. Continuous variables were analyzed using the independent t test and Mann–Whitney U test, as appropriate. Repeated-measures analysis of variance (ANOVA) was applied to identify differences over time between two groups. A P value < 0.05 was considered to be statistically significant.

3. Results

Twenty infants, born at a mean of $29^{+5} \pm 1^{+5}$ weeks gestation with a mean birth weight of 1338 ± 364 g were included in the study. Prenatally, 71 families were approached for parental consent, and 69 approved participations. Overall, 52 infants were excluded, the majority because they were born beyond eligible gestational age for inclusion (Fig. 1). The NIV-NAVA and NCPAP groups were similar in terms of infants' characteristics, with no differences in prenatally administered steroids, Apgar score at 5 min or incidence of premature rupture of the membranes (Table 1). An Edi catheter was inserted when the infants were median (IQR) of 4 (3−6) minutes of age. One infant in the NCPAP group was excluded because of a need to be intubated within 1 h of age, and Edi data were lost of another one infant; thus, two infants were excluded from the analysis of ventilatory and vital sign monitoring data (Fig. 1). The intubation rate and the days on ventilatory support were similar between the groups (Table 2). One infant in the NIV-NAVA group developed pneumothorax. This infant completed two hours of intervention, but was intubated and received surfactant at the age of 2.5 h, because of $FiO_2 > 0.4$. Pneumothorax was diagnosed on the following day during the pressure support ventilation.

The peak and minimum Edi significantly decreased over the first two hours (F = 6.00; P = 0.033 and F = 6.20; P = 0.001, respectively), but there was no difference between the NIV-NAVA and NCPAP groups (F = 0.001; P = 0.98 and F = 0.31; P = 0.59, respectively; Fig. 2). The mean airway pressure and leakages were higher in the NIV-NAVA group than in the NCPAP group (F = 87.81; P < 0.001 and F = 36.05; P < 0.001, respectively). However, nRR, PEEP and FiO_2 did not differ between the two groups (F = 1.13; P = 0.30, F = 0.12; P = 0.73 and F = 0.19; P = 0.67, respectively). SpO_2 and heart rate did not differ between the two groups (F <0.01; P = 0.999 and F = 0.06; P = 0.81, respectively) (Fig. 2). The neural apnea defined as a flat Edi for ≥ 5 s increased over the first two hours (3.0 ± 0.7 and 6.2 ± 1.4 in NIV-NAVA group vs. 10.8 ± 4.2 and 29.1 ± 12.2 in NCPAP group during the 1st and 2nd hour, respectively; F = 6.57; P = 0.021) and were less frequent in the NIV-NAVA group than in the NCPAP group (3.0 ± 0.7 and 6.2 ± 1.4 in NIV-NAVA group vs. 10.8 ± 4.2 and 29.1 ± 12.2 in NCPAP group during the 1st and 2nd hour, respectively; F = 4.69; P = 0.046) (Fig. 3).

Infants who were intubated had a higher FiO_2 than the infants who remained on noninvasive respiratory support (F = 11.16; P = 0.004), without detected differences in nRR, peak or minimum Edi (data not shown). One infant in each group received caffeine citrate during the first two hours.

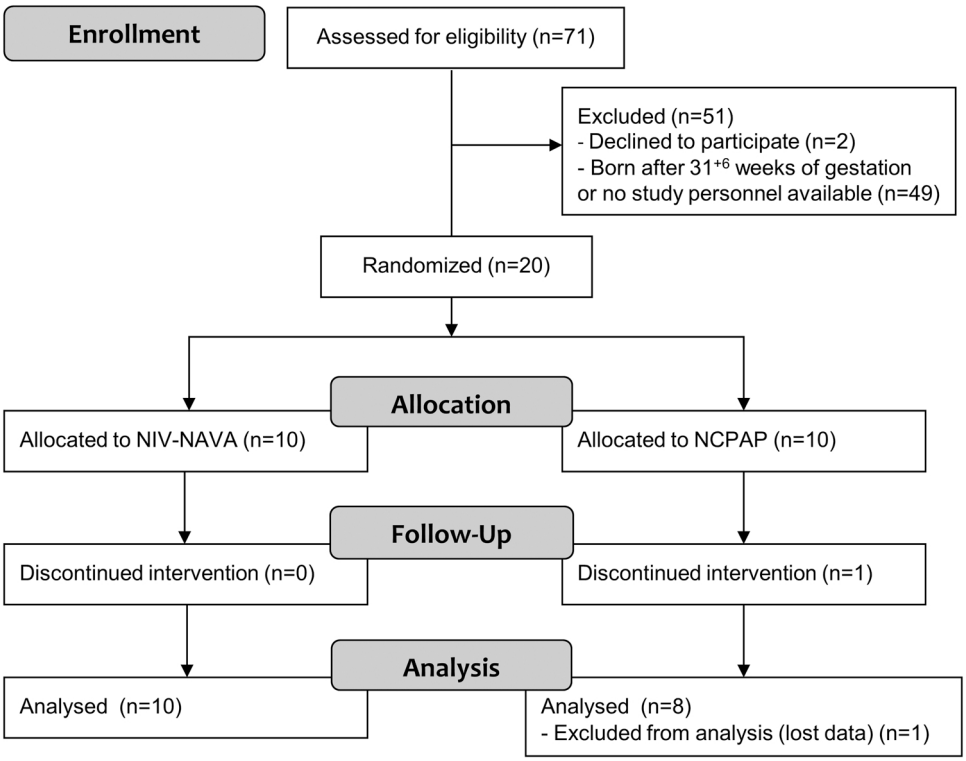

Fig. 1. Flow chart of the study patients.

Table 1
Patient demographic and clinical characteristics.

	NIV-NAVA (n = 10)	NCPAP (n = 10)	P-value
Gestational age, week	$29^{+4} \pm 2^{+0}$	$29^{+6} \pm 1^{+2}$	0.71
Birth weight, gram	1331 ± 370	1346 ± 379	0.93
Small for gestational age	3 (30)	1 (10)	0.26
Male	4 (40)	4 (40)	1.00
Twin	2 (20)	3 (30)	0.61
Prenatal steroids, full dose	9 (90)	9 (90)	1.00
Maternal PROM	3 (30)	4 (40)	0.64
Maternal chorioamnionitis	3 (30)	1 (10)	0.26
Maternal preeclampsia	2 (20)	3 (30)	0.61
Delivery with Cesarean section	7 (70)	7 (70)	1.00
Apgar score at 5 min	9 (7–9)	9 (8–9)	0.63
Umbilical arterial pH	7.30 ± 0.05	7.30 ± 0.05	0.83
Venous pH at NICU admission	7.25 ± 0.06	7.24 ± 0.06	0.91
Venous pCO_2 at NICU admission, kPa	7.98 ± 1.06	7.49 ± 1.27	0.37

Abbreviations: NIV-NAVA, non-invasive neurally adjusted ventilatory assist; NCPAP, nasal continuous positive airway pressure; PROM, premature rupture of membranes; NICU, neonatal intensive care unit.
Values are presented as mean ± SD or n (%).

Table 2
In-hospital pulmonary outcomes.

	NIV-NAVA (n = 10)	NCPAP (n = 10)	P-value
Intubation	3 (30)	4 (40)	1.00
Age at intubation, hour[a]	12.9 (9.8–11.5)	9.9 (3.4–16.3)	0.65
Surfactant	3 (30)	4 (40)	1.00
Pneumothorax	1 (10)	0 (0)	1.00
Invasive ventilation, day[a]	0 (0–3)	0 (0–1)	0.85
Non-invasive ventilation, day	35.5 (9.8–44.8)	25.5 (21.3–37.8)	0.91

NIV-NAVA = non-invasive neurally adjusted ventilatory assist; NCPAP = nasal continuous positive airway pressure.
Data are expressed as n (%) or median (IQR).
[a] calculated for intubated infants, n = 3 and 4, respectively.

4. Discussion

This study did not show any differences in peak or minimum Edi between premature infants randomized to NIV-NAVA or NCPAP support. In both groups, the peak Edi decreased from birth over time during the recorded two hours, indicating that the mode of respiratory support did not affect the breathing effort during the transition.

The Edi signal is considered a respiratory vital sign (Stein and Firestone, 2014), and it provides us with a unique opportunity to investigate breathing patterns and breathing effort (Beck et al., 2011; De Waal et al., 2017; Gibu et al., 2017; Lee et al., 2021a, 2021b, 2015, 2012; Oda et al., 2021; Parikka et al., 2015; Soukka et al., 2014). In neonatal studies, it has been successfully used to compare the effects of different respiratory support modes on breathing (Lee et al., 2015, 2012; Mally et al., 2018; Nasef et al., 2015; Stein et al., 2013). In addition, the Edi signal has been used to assess the favorable effects of prone position, skin-to-skin care and medications on respiratory effort and drive (Kato et al., 2021; Lee et al., 2021b; Parikka et al., 2015; Soukka et al., 2014).

To our knowledge, this is the first study to investigate the use of NIV-NAVA immediately after birth. In previous reports comparing NIV-NAVA and NCPAP in premature infants, randomization occurred after the transition period (Kallio et al., 2019; Latremouille et al., 2021; Yagui et al., 2019). The early insertion of Edi catheters in the present study enabled us to start NIV-NAVA ventilation from a median of 4 min on. We hypothesized that NIV-NAVA would decrease respiratory effort and therefore promote transition. However, the added synchronized pressure support used in this study was not beneficial in reducing the breathing effort, as indicated by similar Edi peak values among the groups. Similarly, the tonic activity of the diaphragm, represented by the Edi minimum, was not affected by the support mode used in this study. This suggested that a PEEP of 6 cmH_2O resulted in enough diaphragm unloading and the establishment of functional residual capacity in

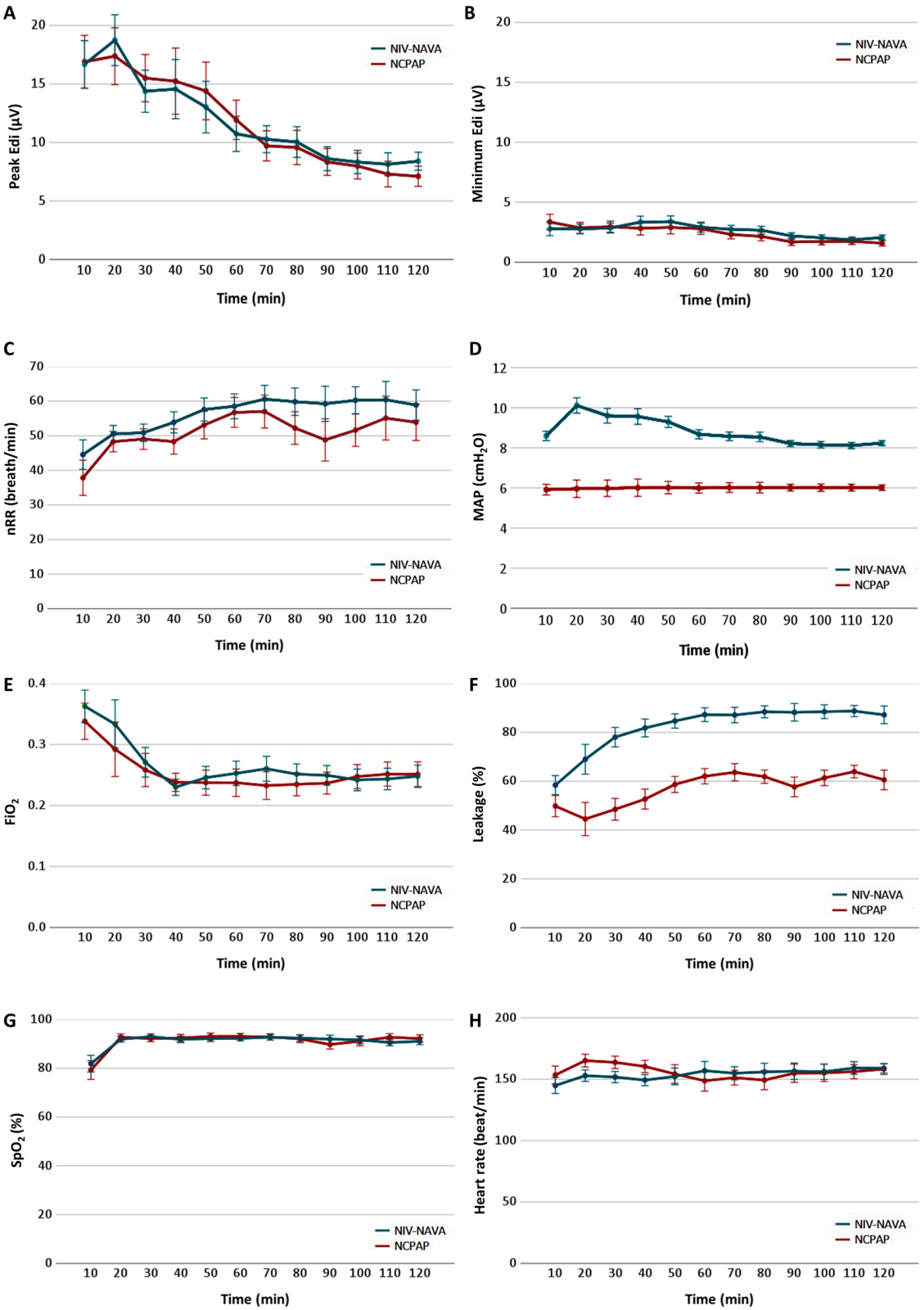

Fig. 2. Peak electrical activity of the diaphragm (Edi) (A), minimum Edi (B), neural respiratory rate (nRR) (C), mean airway pressure (MAP) (D), fraction of inspired O_2 (FiO_2) (E), leakage (F), SpO_2 (G) and heart rate (H) of study patients during the first two hours after birth (n = 18). Green lines denote the NIV-NAVA group (n = 10), and red lines denote the NCPAP group (n = 8). The data are expressed as the means ± SEM. There were no differences in peak Edi, minimum Edi, nRR, FiO_2, SpO_2 and heart rate between two groups. Mean airway pressure and leakages were higher in the NIV-NAVA group than in the NCPAP group ($F = 87.81$; $P < 0.001$ and $F = 36.05$; $P < 0.001$, respectively) in repeated-measures analysis of variance (ANOVA). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

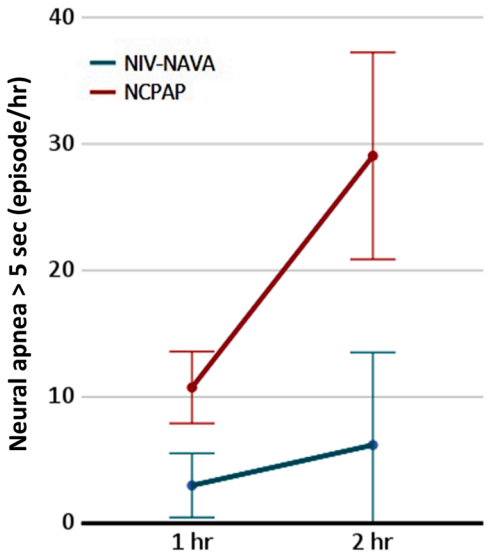

Fig. 3. Neural apnea > 5 sec during the first two hours after birth (n = 18). Green lines denote the NIV-NAVA group (n = 10), and red lines denote the NCPAP group (n = 8). The data are expressed as the means ± SEM. Apneic episodes were 3.0 ± 0.7 and 6.2 ± 1.4 in the NIV-NAVA group. and 10.8 ± 4.2 and 29.1 ± 12.2 in NCPAP group during the 1st and 2nd hour, respectively. The number of apneic episodes increased during the second hour compared to the first hour of life (F = 6.57; P = 0.021). Neural apnea was less frequent in the NIV-NAVA group than in the NCPAP group (F = 4.69; P = 0.046).

included study subjects. Our results indicate that NCPAP might be a sufficient mode of ventilatory support in infants born between 28^{+0} and 31^{+6} weeks gestation when applied during the transition period after birth. Indeed, a recent Cochrane review identified the lack of present data on the effectiveness of NIV-NAVA for the prevention of respiratory failure in the prematurely born population in comparison to other noninvasive respiratory support modes (Goel et al., 2020).

The Edi signal also provided information about the function of the respiratory center immediately after birth (Beck and Sinderby, 2021). There is a lack of knowledge of respiratory drive during the first hours of life. Interestingly, we observed an increase in neural apneic episodes during the second hour of life. The clinical significance of this finding remains, however, unknown. A similar number of neural apneas with the same apnea definition (flat Edi signal for longer than 5 s) has been described among spontaneously breathing preterm infants with a mean age of seven days: average 10 times per hour with range of 2–29 per hour (Beck et al., 2011). Although the reduction of clinical apneic episodes has been reported in synchronized NIPPV compared with NCPAP (Bai et al., 2014; Barrington et al., 2001; Gizzi et al., 2015), this is the first report about the effects of NIV-NAVA on central apnea using Edi signal to identify neural respiration. Compared to chest movements and airflow measures or bradycardia and desaturations to identify apnea (Bai et al., 2014; Barrington et al., 2001; Gizzi et al., 2015; Tabacaru et al., 2019b), Edi signal is a direct and reliable method. We defined neural apnea as a flat Edi signal for more than 5 sonds. After a 5-second apnea, the NIV-NAVA was set to deliver backup breaths. Fewer neural apneic episodes during NIV-NAVA compared to NCPAP may indicate that NIV-NAVA stimulates respiratory drive or that the reduction of apneic episodes is caused by an accomplished higher mean airway pressure compared to NCPAP. Although caffeine citrate reduces Edi signal-based neural apnea in preterm infants (Parikka et al., 2015), it is unlikely to play a role in our study since only one infant in each group received caffeine citrate during the study period. The difference in neural apneic episodes did not contribute to the need for supplemental oxygen or intubation in our study.

Leakages were higher in the NIV-NAVA group than in the NCPAP group, probably due to intermittent positive pressure delivery. Higher leakage at the nasal interface may generate discomfort and may also stimulate breathing. However, there was no difference in respiratory rates and peak Edi which were known to correlate with pain and discomfort scales in preterm infants (Nam et al., 2019). Previous studies have shown that NIV-NAVA improved patient-ventilatory synchrony and effectively reduced diaphragm work of breathing even in the presence of large leakages (Beck et al., 2009; Lee et al., 2015; Matlock et al., 2020). The leakage levels of the NIV-NAVA group of our study (Fig. 2) were comparable or lower than in other studies of very preterm infants: 75% (Beck et al., 2009) and 87.6 ± 8.3% (Lee et al., 2015). One case of pneumothorax in the NIV-NAVA group may raise concerns about air leaks. However, since pneumothorax occurred during the pressure support mode one day after intubation, it is difficult to conclude that the higher leakage during the first 2 h with NIV-NAVA was related to this air leak.

The main limitation of this trial was the small number of study patients, which prevented us from evaluating the possible effects of interventions on clinical outcomes. A large portion of recruited babies ended up being born beyond the inclusion age prolonged the recruitment period. Because of our small study sample size, we used information from the Edi signal to evaluate the clinical effect of NIV-NAVA as a surrogate outcome. The clinical significance of a reduced number of apneas with immediate NIV-NAVA support needs to be shown in a randomized controlled trial with a higher number of premature infants. In addition, this study did not provide data for higher levels of NAVA support or for extremely preterm infants.

5. Conclusion

NIV-NAVA applied immediately after birth was equal to NCPAP in infants born between 28^{+0} and 31^{+6} gestational weeks regarding peak Edi and total days of ventilatory support. We found no group differences in breathing effort, nRR, or the need for supplemental oxygen or respiratory outcomes. However, NIV-NAVA reduced neural apneic episodes compared to NCPAP. In the future, more studies are needed to identify which groups of preterm infants and at what age would benefit from NIV-NAVA support.

Conflict of interest

Arata Oda has received financial support from the Getinge company and the Fukuda Denshi company during his research time. The Edi catheters used in this study and the analyses software was provided by the Getinge company. Liisa Lehtonen and Hanna Soukka have given academic lectures about NAVA in several scientific conferences, and they have been supported by the Getinge company and the Fukuda Denshi company. Juyoung Lee, Vilhelmiina Parikka and Linda Wallström have nothing to disclose.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

Juyoung Lee: Data curation, Validation, Formal analysis, Visualization, Writing – original draft preparation. **Vilhelmiina Parikka:** Methodology, Investigation, Writing – review & editing. **Arata Oda:** Conceptualization, Methodology, Software, Investigation, Data curation. **Linda Wallström:** Data curation, Writing – original draft preparation. **Liisa Lehtonen:** Conceptualization, Methodology, Funding acquisition, Supervision, Writing – review & editing. **Hanna Soukka:** Conceptualization, Methodology, Software, Investigation, Data curation, Supervision, Project administration, Writing – review & editing. All authors read and approved the final version of the manuscript.

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