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Backup ventilation during neurally adjusted ventilatory assist in preterm infants

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Abstract

Objective: To analyze the proportion of backup ventilation during neurally adjusted ventilatory assist (NAVA) in preterm infants at different postmenstrual ages (PMAs) and to analyze the trends in backup ventilation in relation to clinical deteriorations.

Methods: A prospective observational study was conducted in 18 preterm infants born at a median (range) 27^{+4} (23^{+4}–34^{+4}) weeks of gestation with a median (range) birth weight of 1,100 (460–2,820) g, who received respiratory support with either invasive or noninvasive NAVA. Data on ventilator settings and respiratory variables were collected daily; the mean values of each 24-h recording were computed for each respiratory variable. For clinical deterioration, ventilator data were reviewed at 6-h intervals for 30 h before the event.

Results: A total of 354 patient days were included: 269 and 85 days during invasive and noninvasive NAVA, respectively. The time on backup ventilation (%/min) significantly decreased with increasing PMA during both invasive and noninvasive NAVA. The neural respiratory rate did not change over time. The median time on backup ventilation was less than 15%/min, and the median neural respiratory rate was more than 45 breaths/min for infants above 26^{+0} weeks PMA during invasive NAVA. The relative backup ventilation significantly increased before the episode of clinical deterioration.

Conclusion: The proportion of backup ventilation during NAVA showed how the control of breathing matured with increasing PMA. Even the most immature infants triggered most of their breaths by their own respiratory effort. An acute increase in the proportion of backup ventilation anticipated clinical deterioration.

KEYWORDS

clinical deterioration, infant pulmonary function, interactive ventilatory support, mechanical ventilation, respiratory mechanics, ventilator weaning

1 | INTRODUCTION

Neurally adjusted ventilatory assist (NAVA) has been developed and evaluated in many studies, including studies of preterm infants, over the last decade. This technique uses the electrical activity of the diaphragm (Edi) to control respiratory support and the NAVA level as an amplification factor that converts the Edi signal into a proportional pressure.[1] NAVA synchronizes mechanical breaths with the patient's neural respiratory drive and supports this drive proportionally to its effort.[1–3] Several studies have demonstrated that

the patient-ventilator interaction is improved and that delivered pressure is decreased with NAVA compared with other conventional modes in preterm infants.[4–9]

NAVA uses the patient's own respiratory effort as both a trigger and an assist control during respiratory support.[1,10] Because of these characteristics, many clinicians are concerned if the weak respiratory effort of preterm infants would hinder NAVA working efficiently for them.[11–14] This is one of the important obstacles causing hesitation regarding the use of NAVA in preterm infants. Additionally, there is a paucity of research on the use of NAVA in the most immature preterm infants.

We aimed to investigate the success of NAVA ventilation at different postmenstrual ages (PMAs) in preterm infants by analyzing the proportion of backup ventilation during NAVA. In addition, the trends in backup ventilation were analyzed in relation to clinical deteriorations.

2 | MATERIALS AND METHODS

A prospective observational study took place from March 2020 to December 2020 in the Level III neonatal intensive care unit of Turku University Hospital, Finland. We included preterm infants born before 36 weeks of gestation who received at least 24 h of ventilatory support with invasive or noninvasive NAVA using Servo-i or Servo-n ventilators (Getinge).

As NAVA was the primary ventilation mode in this unit, for intubated preterm infants, we began NAVA whenever the infants had spontaneous breathing. As soon as possible we extubated them and applied noninvasive NAVA. Caffeine was administered if infants had significant apnea or were supported with NAVA. To start and discontinue caffeine was decided on clinical basis by the assigned clinicians. Before the start of NAVA mode, a standard feeding tube was replaced with a dedicated electrode-equipped catheter to detect Edi (Edi catheter; Getinge). The trigger Edi level was set as 0.5 μV above the minimum Edi. Attending clinicians decided and adjusted the NAVA level, positive end-expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2), and backup ventilation (pressure control mode) settings according to the infant's condition. The apnea time was set as 2–10 s. It was determined according to each patient's pulmonary status, respiratory drive, and the severity of desaturation and bradycardia during apnea. After the set apnea time without the Edi signal, the backup ventilation started with a preset peak pressure and frequency until the Edi trigger resumed. Our usual backup rate was set as 20–40 breaths/min and the inspiratory time was set as 0.4–0.5 s. The safety limit for peak inspiratory pressure (PIP) was set as 25–35 cmH_2O. If the infant lost his/her cardiorespiratory stability during NAVA, the ventilator mode was changed, and this episode was defined as "clinical deterioration." Except for these cases, invasive NAVA was continuously used with adjusting NAVA levels until the infant was extubated to noninvasive NAVA. Noninvasive NAVA was also continued with adjusting NAVA levels until the infant was reintubated to invasive NAVA or weaned to nasal continuous positive airway pressure or high-flow nasal cannula. Discontinuing NAVA was decided at the discretion of the medical team.

For the infant participating in the study, ventilator settings and respiratory variables were recorded every day and exported to a specific computer using Servo Record Viewer version 1.0 (Maquet Critical Care AB; Getinge). The collected data provided the values for PIP, mean airway pressure, PEEP, expiratory tidal volume, peak Edi, minimum Edi, measured respiratory rate (RR), neural respiratory rate (nRR), and percentage time spent in backup ventilation for each minute. All the ventilator data were inspected and compared with the event logs recorded automatically from the ventilator, which included all alarm notifications, mode and setting changes, cable connections, and disconnections. Data during disconnection of the Edi cable, malfunction, or dislocation of the Edi catheter were excluded from the analysis. The mean values during each day were computed for each ventilatory variable. If there was a change in the ventilatory setting parameters, we chose the parameter that was applied for a longer duration in the 24-h time period. For clinical deterioration, ventilator data 30 h before the episode were reviewed at 6-h intervals. The zero time point was defined as the moment when the ventilator mode was switched from NAVA to others because of clinical deterioration.

The following data were collected from medical records: gestational age at birth, birth weight, sex, PMA, and body weight at the study date. For clinical deterioration, information about its cause and interventions were collected. The study was approved by the Ethics Committee of the Hospital District of Southwest Finland as well as by the scientific research committee of the Pediatric Department of Turku University Hospital, Finland. Written informed consent was obtained from both parents according to the guidelines of the Research and Ethics Board before patient enrollment in this study.

The median values of time on backup ventilation and nRR were compared according to increasing PMAs using the linear mixed model repeated measures analysis with measurement nested within subject as random effect. Changes in the proportion of backup ventilation before clinical deterioration were analyzed using the Friedman test. A p value < .05 was considered to be statistically significant. Statistical analyses were performed using SPSS v27.0 (IBM).

3 | RESULTS

Eighteen preterm infants born at a median (range) 27^{+4} (23^{+4}–34^{+4}) weeks of gestation with a median (range) birth weight of 1,100 (460–2,820) g were included in the study. A total of 354 patient days of ventilator data were collected: 269 patient days during invasive NAVA and 85 patient days during noninvasive NAVA. The percentage of excluded data was a median (IQR) of 0.8% (0.4%–1.6%) per each patient day: 0.9% (0.4%–1.7%) during invasive NAVA and 0.7% (0.3%–1.0%) during noninvasive NAVA. Information of each patient day and ventilator settings at the time of data collection are described in Table 1. On the day of data collection, the infant's age in

TABLE 1 Information of each patient day at the time of data collection

	Total (n = 354)	Invasive NAVA (n = 269)	Noninvasive NAVA (n = 85)
Day of life, day	43 (1–90)	36 (1–90)	53 (3–87)
Postmenstrual age, week	31^{+6} (24^{+2}–36^{+6})	31^{+3} (24^{+2}–36^{+6})	33^{+6} (24^{+2}–36^{+1})
Body weight, g	1,430 (550–3,260)	1,370 (550–3,260)	1,655 (645–3,070)
Caffeine, n (%)	320 (90.4)	243 (90.3)	77 (90.6)
Ventilator setting			
FiO_2, %	30 (21–68)	30 (21–68)	28 (21–65)
PEEP, cmH_2O	6 (4–8)	6 (4–8)	6 (4–8)
NAVA level, $cmH_2O/\mu V$	1.5 (0–2.5)	1.5 (1.0–2.5)	1.2 (0–2.0)
PIP limit, cmH_2O	35 (20–65)	30 (25–35)	57 (20–65)
Apnea time, s	3 (2–10)	3 (2–10)	5 (2–10)
Backup rate, per min	30 (16–40)	30 (16–40)	30 (16–30)

Note: Values are median (range).

Abbreviations: FiO_2, fraction of inspired oxygen; NAVA, neurally adjusted ventilatory assist; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure.

days, PMA, and body weight ranged from 1 to 90 days, 24^{+2} to 36^{+6} weeks, and 550–3260 g, respectively. About 90% of infants received caffeine at the time of data collection. Their median (range) NAVA level was 1.5 (0–2.5) $cmH_2O/\mu V$. The preset median (range) apnea time and backup ventilation during apnea were 3 (2–10) s and 30 (16–40) breaths per minute, respectively (Table 1).

During invasive NAVA, the time on backup ventilation (%/min) significantly decreased according to an increase in PMA (F = 18.17, fixed effect estimates −3.1, 95% CI −4.6 to −1.6, $p < .001$). The median time on backup ventilation decreased from 25.1%/min for infants below 26^{+0} weeks PMA to less than 15%/min for infants above 26^{+0} weeks PMA (Figure 1A). Although the median nRR increased from 33 breaths/min for infants below 26^{+0} weeks PMA to more than 45 breaths/min in infants above 26^{+0} weeks PMA (Figure 1B), the change of nRR over time was not statistically significant (F = 0.283, fixed effect estimates 0.57, 95% CI −1.6 to 2.7, $p = .597$). Several outliers were found in both percentage time on backup ventilation and nRR in most PMA groups.

During noninvasive NAVA, the time on backup ventilation (%/min) significantly decreased according to an increase in PMA (F = 21.693, fixed effect estimates −1.5, 95% CI −2.3 to −0.8, $p = .002$). The median time on backup ventilation decreased from 5.6%/min to less than 3%/min (Figure 1C). However, nRR did not show significant changes over increasing PMA (F = 0.080, fixed effect estimates 0.5, 95% CI −3.2 to 4.3, $p = .781$) (Figure 1D).

There were seven episodes of clinical deterioration in six patients. The episodes were caused by hemodynamically significant patent ductus arteriosus, clinical sepsis, ventilator-associated pneumonia, and necrotizing enterocolitis (Table 2). Relative backup ventilation significantly increased up to the episode of clinical deterioration (Figure 2). The percentage of backup ventilation increased by 1.3 (0.8–2.0) fold from 24 to 18 h, 1.7 (1.2–3.1) fold from 18 to 12 h, 2.0 (1.3–4.6) fold from 12 to 6 h, and 3.4 (2.3–6.4) fold from 6 to 0 h before the episodes compared to the baseline (Friedman test's $\chi^2 = 20.69$, $p < .001$). After stabilization, all six infants returned to NAVA support.

Except for the seven episodes described above, ventilatory support with invasive NAVA continued without interruptions until extubation. Noninvasive NAVA was changed to invasive NAVA if the infant needed intubation or discontinued when the infant stabilized to cope with nasal continuous positive airway pressure or high-flow nasal cannula.

4 | DISCUSSION

This study demonstrated that the proportion of backup ventilation decreased with increasing PMA, especially after 26 weeks. However, even the most immature infants triggered most of the ventilator breaths by their own respiration. An increase in the proportion of backup breaths anticipated clinical deteriorations, thereby showing the clinical value of observing the trends of backup ventilation.

Preterm infants have immature respiratory control leading to apnea.[15,16] With increasing myelination of the brainstem, respiratory effort becomes stronger, and the number of apnea decreases.[15–17] Postnatal maturation of the respiratory center explains our results: the decrease in backup ventilation with increasing PMA. Our study showed that nRRs were already in the physiologic range of 40–60 breaths per minute, and the proportion of backup breaths was very

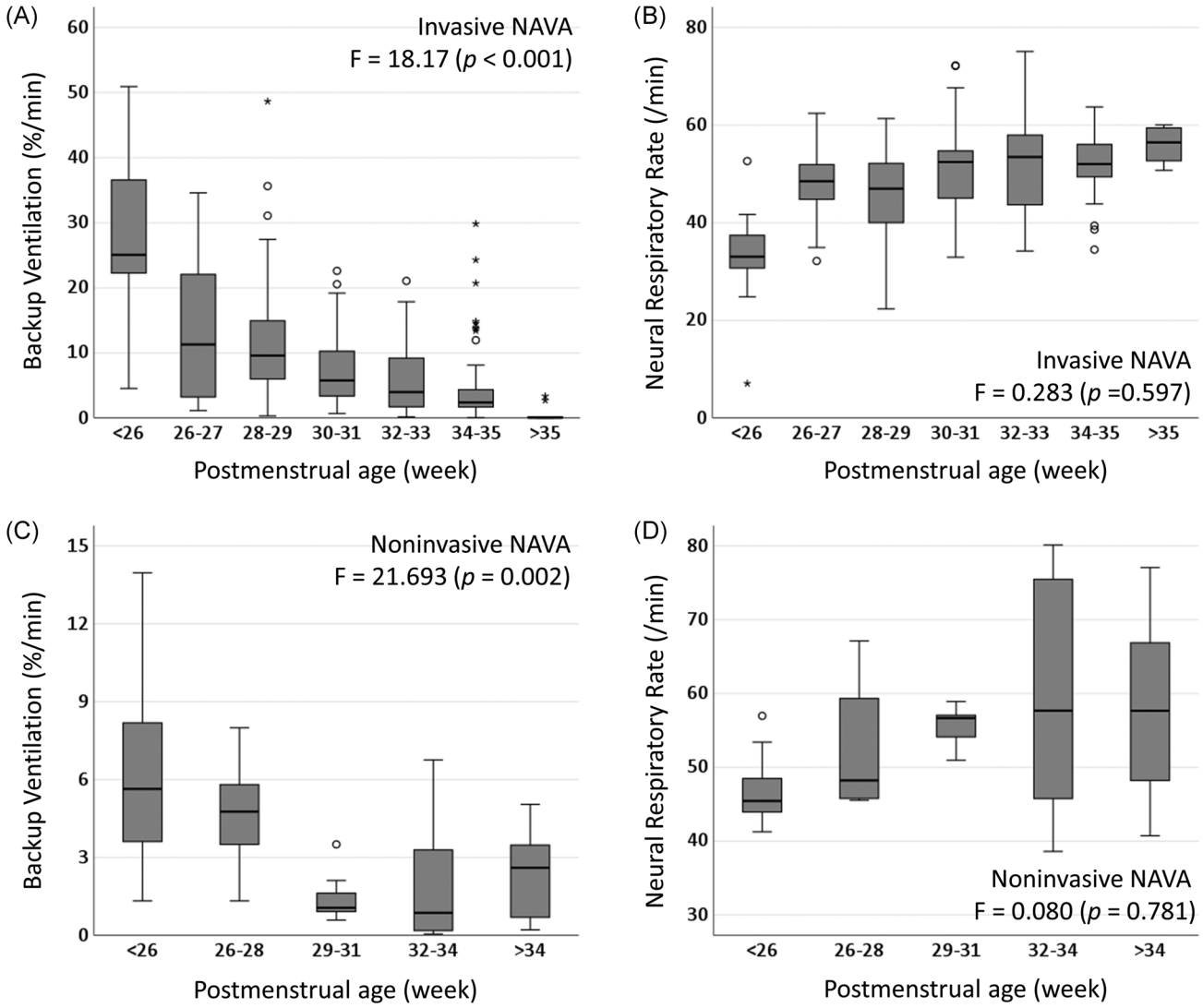

FIGURE 1 Time percentage on backup ventilation and neural respiratory rate according to postmenstrual age (PMA) during invasive and noninvasive neurally adjusted ventilatory assist (NAVA). The linear mixed model repeated measures analysis was used with measurement nested within subject as random effect. For invasive NAVA, each PMA group included 17, 22, 52, 60, 66, 43, and 9 patient days. For noninvasive NAVA, each PMA group included 9, 8, 9, 35, and 24 patient days. Box plots show median (IQR), minimum, and maximum values

low from 26 weeks PMA. This justifies the implementation of NAVA from a very early PMA.

The development of neural respiratory control could be demonstrated because the study population was supported with NAVA rather than other controlled ventilatory modes. In previous studies, controlled mechanical ventilation led to diaphragmatic dysfunction and prolonged ventilation, whereas patient-triggered ventilation prevented diaphragm weakness and maintained spontaneous breathing activity.[18–22] Since NAVA supports infant's own respiration synchronized with the Edi and provides backup ventilation only during neural apnea, it would be ideal for preventing diaphragm weakness and strengthening their respiratory effort.

This is the first study to provide information about the typical amount of backup ventilation in preterm infants at different PMA. However, the amount of backup ventilation is affected by a set apnea time and a backup rate during NAVA. Choosing an optimal apnea time and a backup rate is important to avoid hypo-/hypercarbia in premature infants.[23] These parameters should be chosen and adjusted according to each infant's age and clinical condition. In our study, the median apnea time was 3 and 5 s for invasive and noninvasive NAVA, respectively, and the median backup rate was 30 breaths per minute for both. The included infants remained stable with these settings except during their clinical deteriorations.

As the NAVA mode is based on the patient's own respiratory drive, it is inevitably sensitive to detect an increase in apnea, which is the most common symptom of clinical deterioration in preterm infants. The current ventilators operating NAVA display trends in the proportion of backup ventilation and nRR for the last 24 or 72 h. These trends can be useful to detect early signs of clinical deterioration in this vulnerable population.

TABLE 2 Details of episodes of clinical deteriorations ($n = 7$)

Patient number	DOL (day)	Time	PMA (week)	Weight (g)	Diagnosis	Intervention	Changes on ventilator mode and settings
04	5	17:30	24^{+5}	680	HS-PDA	Indomethacin therapy	NAVA (FiO_2 0.21, PEEP 6 cmH_2O, NAVA level 1.2 $cmH_2O/\mu V$) → SIMV (FiO_2 0.3, PEEP 6/PIP 18 cmH_2O, RR 30/min)
04	13	01:57	25^{+6}	740	Clinical sepsis	Antibiotic therapy	NAVA (FiO_2 0.23, PEEP 7 cmH_2O, NAVA level 2.0 $cmH_2O/\mu V$) → SIMV (FiO_2 0.3, PEEP 7/PIP 20 cmH_2O, RR 40/min)
05	18	07:47	26^{+0}	760	Clinical sepsis	Antibiotic therapy	NAVA (FiO_2 0.33, PEEP 6 cmH_2O, NAVA level 2.0 $cmH_2O/\mu V$) → SIMV (FiO_2 0.5, PEEP 6/PIP 23 cmH_2O, RR 40/min)
06	8	11:10	24^{+4}	590	HS-PDA	Indomethacin therapy	NAVA (FiO_2 0.33, PEEP 6 cmH_2O, NAVA level 2.0 $cmH_2O/\mu V$) → SIMV (FiO_2 0.5, PEEP 6/PIP 23 cmH_2O, RR 40/min)
07	6	23:40	27^{+3}	810	Clinical sepsis	Antibiotic therapy	NAVA (FiO_2 0.27, PEEP 6 cmH_2O, NAVA level 2.0 $cmH_2O/\mu V$) → SIMV (FiO_2 0.38, PEEP 6/PIP 20 cmH_2O, RR 40/min)
14	63	13:48	36^{+1}	2890	VAP	Antibiotic therapy	NAVA (FiO_2 0.45, PEEP 6 cmH_2O, NAVA level 1.8 $cmH_2O/\mu V$) → SIMV (FiO_2 0.50, PEEP 6/PIP 22 cmH_2O, RR 20/min)
16	29	03:40	27^{+6}	785	NEC	No enteral feeding, antibiotic therapy, laparotomy	NAVA (FiO_2 0.40, PEEP 8 cmH_2O, NAVA level 2.0 $cmH_2O/\mu V$) → HFO (FiO_2 1.0, MAP 13 cmH_2O, Amplitude 42 cmH_2O, 12 Hz)

Abbreviations: DOL, day of life; FiO_2, fraction of inspiratory oxygen; HFO, high-frequency oscillation; HS-PDA, hemodynamically significant patent ductus arteriosus; MAP, mean airway pressure; NAVA, neurally adjusted ventilatory assist; NEC, necrotizing enterocolitis; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; PMA, postmenstrual age; RR, respiratory rate; SIMV, synchronized intermittent mandatory ventilation; VAP, ventilator-associated pneumonia.

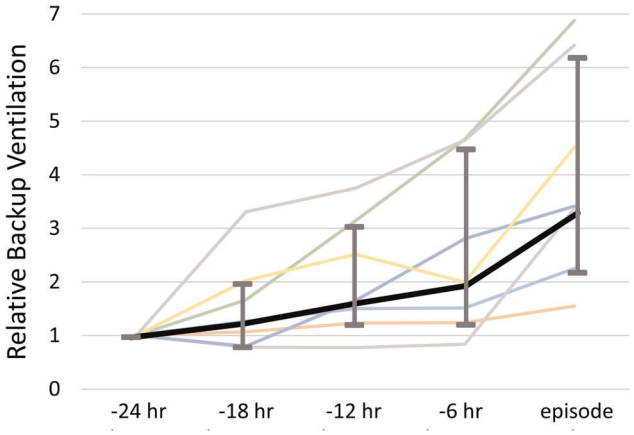

FIGURE 2 Relative ratio of time on backup ventilation compared to the baseline of 24 h before the episode (−24 h). Values are medians (IQRs) of the previous 6 h. Faint lines indicate individual changes. Values at each time point are 1.3 (0.8 – 2.0), 1.7 (1.2 – 3.1), 2.0 (1.3 – 4.6), and 3.4 (2.3 – 6.4), respectively. Friedman test's χ^2 was 20.69 ($p < .001$) [Color figure can be viewed at wileyonlinelibrary.com]

This study has weaknesses inherent to observational studies. First, each PMA group was heterogeneous in terms of the severity of respiratory distress and length of mechanical ventilation. However, our sample came from approximately 1 year of patient days (354) and included almost half of all ventilated preterm infants in a level III neonatal intensive care unit during the study period. Second, we analyzed the ventilator data based solely on PMA, not on gestational age when infants were born, because the number of infants was too small to analyze those separately. However, spontaneous respiration and the backup ventilation portion may be affected by both gestational age and PMA. Third, because we collected data for mechanically ventilated patients, the majority of study recordings were from infants having bronchopulmonary dysplasia, and they do not represent all preterm neonates. However, since they are the target population of ventilator care, it is meaningful to understand the developmental changes in their neural respiratory drive and the significance of an acute increase in backup ventilation.

In conclusion, we used the proportion of backup ventilation during NAVA to show how the control of breathing matured with increasing PMA in preterm infants. It is important that even the most immature infants triggered most of their breaths by their own respiration. As an acute increase in the proportion of backup ventilation anticipated clinical deterioration, we identified the trends in backup ventilation as a useful tool to detect early warning signs of clinical deterioration in preterm infants.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Juyoung Lee conceptualized and designed the study, collected data, carried out analyses, and drafted the manuscript. Vilhelmiina Parikka collected data and reviewed and revised the manuscript. Liisa Lehtonen reviewed and revised the manuscript for important intellectual content. Hanna Soukka participated in the design of the study, collected data, reviewed and revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

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

ETHICAL APPROVAL

Informed parental consents were obtained before study participation and the study was approved by the Ethics Committee of Hospital District of Southwest Finland (approval number TO8/004/20); clinicaltrials.gov registration number NCT04659083.

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