Impact of High Flow Nasal Cannula Therapy on Oral Feeding in Very Low Birth Weight Infants with Chronic Lung Disease

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Abstract: Previous studies on high-flow nasal cannula (HFNC) in very-low-birth-weight infants (VLBWIs) focused on comparing HFNC with nasal continuous positive airway pressure (nCPAP) to determine the usefulness of HFNC as a backup in the case of extubation failure and nasal trauma; however, the studies did not consider oral feeding. This retrospective case-control study aimed at elucidating whether HFNC could prevent the delay in feeding and achievement of full oral feeding in VLBWIs with chronic lung disease (CLD). Forty five VLBWIs were enrolled in this study: an HFNC group (n = 11) that was supported by HFNC at oral feeding initiation, and a non-HFNC group (n = 34) that could start oral feeding without HFNC. The gestational age and birth weight of the HFNC group were lower than those in the non-HFNC group. The median duration of exposure to oxygen and neonatal intensive care unit stay were comparable in both groups. The timings of oral feeding initiation and full oral feeding achievement in both groups were not significantly different: 35.3 (33.0 – 38.1) vs. 35.5 (33.7 – 42.4) weeks (P = 0.91) for the HFNC and 38.6 (34.4 – 42.3) vs. 36.7 (34.6 – 44.4) weeks postmenstrual age (P = 0.29) for the non-HFNC. Clinically significant aspiration pneumonia during the period of oral feeding was not observed in the HFNC group. Respiratory support by HFNC in VLBWIs with CLD might prevent oral feeding delay. Initiation of oral feeding of VLBWIs on HFNC might be safe and might accelerate the achievement of oral feeding milestones.

Keywords: high-flow nasal cannula, oral feeding, chronic lung disease, preterm infant, very low birth weight infants.

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Introduction

A heated, humidified high-flow nasal cannula (HFNC) is a mode of respiratory support that delivers blended gas at a flow rate of 2 – 8 l/min, which is lower than that of nasal continuous positive airway pressure (nCPAP) [1]. nCPAP is effective in preventing intubation in preterm very-low-birth-weight infants (VLBWIs) or in cases of extubation failure after mechanical ventilation [2]. Although its side effects include gaseous distension of the bowel, nasal trauma, and nasal deformity [3], HFNC is well tolerated and easy to apply in preterm VLBWIs, and is commonly used as a noninvasive mode of respiratory support in the neonatal intensive care unit (NICU) [4, 5]. Previous studies on HFNC in VLBWIs focused mainly on comparison with nCPAP to determine the usefulness of HFNC as a backup in cases of extubation failure and nasal trauma [6–9].
Preterm VLBWIs should be able to take oral feeding from 34 weeks postmenstrual age (PMA) [10], as by that time they have acquired coordination of sucking, swallowing, and respiration during feeding. In general, VLBWIs are at risk of chronic lung disease (CLD), and most of them require positive-pressure respiratory support, even after 34 weeks PMA. Because of CLD, they usually lag in oral feeding initiation, despite oral feeding stimulation [11, 12]. Oral feeding difficulties often affect their ability to achieve independent oral feeding and result in prolonged hospital stay.

In an adult study, HFNC enabled continuation of oral intake without aspiration during oxygen therapy [13]; therefore we hypothesized that infants who require HFNC after 34 weeks can orally feed in the same manner as those who do not require HFNC. A few studies have addressed feeding in preterm VLBWIs supported by HFNC because of CLD [14–16]. This study was designed to elucidate whether HFNC in VLBWIs with CLD could prevent the delay in feeding opportunities and achieve full oral feeding.

**Methods**

This is a retrospective case-control study in which admitted to the NICU in the Hospital of the University of Occupational and Environmental and Health, Japan between April 2013 and September 2016 were enrolled. Of the 63 VLBWIs, 18 infants were excluded because some had a congenital heart disease or anomalies, some were transferred to other hospitals, and some died (Fig. 1). Of the 45 eligible infants, 20 required invasive mechanical ventilation during the early neonatal period; the remaining 25 were cared for by nCPAP.

Our routine practice for VLBWIs with respiratory distress after extubation is as follows: We introduce nCPAP with an initial pressure of 6 cmH2O, then subsequently switch to HFNC if the respiratory condition stabilizes with a supplementary oxygen requirement of less than 30% (fraction of inspiratory oxygen 0.3) or if the nursing team judges the infants as not tolerating nCPAP because of nasal trauma after a few weeks of nCPAP therapy. An HFNC (Optiflow Junior™ infant) is used at 2 l/kg/min with 21–30% of oxygen, depending on each infant’s requirement. If any infant

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**Fig. 1. Flowchart to select infants who were eligible for the study.** HFNC: high-flow nasal cannula, nCPAP: continuous positive airway pressure, VLBWI: very-low-birth-weight infant, NICU: neonatal intensive care unit.
becomes clinically stable on the HFNC, we wean it off at a reduction rate of 1–2 l/min in 24–72 h. We switch from the HFNC to nCPAP if any infant shows increased breathing effort or oxygen requirement. In this study, we defined the HFNC group \((n=11)\) as infants who were supported by HFNC at the initiation of oral feeding, and the non-HFNC group \((n=34)\) as infants who could start oral feeding without HFNC (Fig. 1). As a routine practice, we did not begin oral feeding in infants on nCPAP, but only in infants who began breathing stably after 34 weeks PMA, regardless of the use of HFNC after oral feeding skill evaluation by physical therapists. Infants were judged to have achieved full oral feeding when they could consume the indicated amount of milk without tube feeding. CLD was defined as the duration of oxygen therapy being more than 28 days after birth or 36 weeks PMA. Our study was approved by the institutional review board of the University of Occupational and Environmental Health, Japan.

**Statistical Analyses**

We used Fisher’s exact test to compare the HFNC and non-HFNC groups on proportions of sex, gestational age, birth weight, postnatal surfactant, and CLD at 28 days of life and at 36 weeks PMA. The Mann–Whitney \(U\) test was used for comparing the HFNC and non-HFNC groups on the timings of the first and of full oral feeding, the duration of hospital stay and exposure to oxygen, and Apgar scores (1 and 5 min). The differences were considered significant at \(P<0.05\). All statistical analyses were performed using the GraphPad Prism 6 statistics software package.

**Results**

Demographic and clinical characteristics of the study subjects are presented in Table 1. The HFNC group showed a lower gestational age (27.4 vs. 31.2 weeks PMA, \(P=0.017\)) and a lower birth weight (905 vs. 1,293 g, \(P=0.004\)) than the non-HFNC group. We evaluated that the HFNC group had more immature respiratory function, because there were significant differences in using surfactant (82% vs. 44%, \(P=0.03\)). During the early neonatal period (\(P=0.14\)), 7 of the 11 infants in the HFNC group (63.6%) and 13 of the 34 infants in the non-HFNC group (38%) required invasive respiratory support for respiratory distress, indicating greater immature ability of respiration in the HFNC group. In addition, there was a significant difference in CLD morbidity at 36 weeks PMA (82% vs. 9%, \(P<0.01\)) between the HFNC and non-HFNC groups.

| Characteristics                                      | HFNC \((n=11)\) | Non-HFNC \((n=34)\) | \(P\)-value |
|------------------------------------------------------|----------------|---------------------|------------|
| Gender, male                                         | 4 (36.4)       | 20 (58.8)           | 0.17       |
| Gestational age (weeks)                              | 27.4 (23.1–32.0) | 31.2 (23.7–39.6)    | 0.02       |
| Birth weight (g)                                     | 905 (379–1,141) | 1,293 (428–1,498)   | <0.01      |
| Postnatal surfactant                                 | 9 (82)         | 15 (44)             | 0.03       |
| Mechanical ventilation                               | 7 (63.6)       | 13 (38)             | 0.14       |
| CLD at 28 days                                       | 9 (82)         | 17 (50)             | 0.27       |
| CLD at 36 weeks PMA                                   | 9 (82)         | 3 (9)               | <0.01      |
| Duration from birth to the timing of the first oral feeding (days) | 52 (14–97)     | 31.5 (1–88)         | 0.07       |
| Duration from birth to the timing of full oral feeding (days) | 77 (26–117)    | 38 (9–129)          | 0.03       |
| Use of oxygen during oral feeding                     | 4 (36.4)       | 11 (32.3)           | 0.67       |

Data are represented as median (range) or \(n\) (%). HFNC: high-flow nasal cannula, CLD: chronic lung disease. Data were analyzed using the Mann–Whitney \(U\) or Fisher’s exact test.
no side effects (nasal trauma, pneumothorax etc.) in either group. The HFNC group did not require switching to nCPAP because of respiratory failure, and no clinically significant aspiration pneumonia was observed in the HFNC group during oral feeding. Eleven of the 34 infants (32.3%) in the non-HFNC group and 4 of 11 (36.4%) in the HFNC group used oxygen when they had begun to take oral, with no difference between the groups \( (P = 0.67) \). Only 2 infants in the non-HFNC group, who had hyperinsulinemia, had to use intravenous hyperalimentation when they began to take oral feeding.

The timings of the first and of full oral feeding in the two groups are compared in Fig. 2. Although the HFNC group was more immature than the non-HFNC group in terms of gestational age and birth weight, as shown in Table 1, there was no significant difference in the timing of the first oral feeding between the two groups: 35.3 (33.0 \( \pm \) 38.1) vs. 35.5 (33.7 \( \pm \) 42.4) weeks PMA, respectively; \( P = 0.91 \). The timings of achievement of full oral feeding were also similar: 38.6 (34.4 \( \pm \) 42.3) vs. 36.7 (34.6 \( \pm \) 44.4) weeks PMA, respectively; \( P = 0.29 \). There was also no difference between the two groups in duration from birth to the timings of the first oral feeding: 52 (14 \( \pm \) 97) vs. 31.5 (1 \( \pm \) 88) days, respectively; \( P = 0.07 \).

The timings of the full oral feeding in the non-HFNC group were earlier than that in the HFNC group: 77 (26 \( \pm \) 117) vs. 38 (9 \( \pm \) 129) days, respectively; \( P = 0.03 \).

The median duration of exposure to oxygen (A) and PMA at discharge from the NICU (B) are presented in Fig. 3. Despite a greater immature ability of respiration in the HFNC group, there was no significant difference in duration of exposure to oxygen and PMA at discharge from the NICU between the HFNC and non-HFNC groups: Exposure to oxygen: 3 (0 \( \pm \) 255) vs. 2 (0 \( \pm \) 126) days, respectively; \( P = 0.97 \), PMA at discharge from the NICU: 42.4 (39.7 \( \pm \) 65.1) vs. 41.4 (37.3 \( \pm \) 56.3) weeks PMA, respectively; \( P = 0.197 \).

**Discussion**

To our knowledge, this is the first report indicating that HFNC might prevent the delay in feeding opportunities and achievement of full oral feeding for prenatal infants needing non-invasive ventilation support. In this study, whereas the HFNC group was more immature and had more CLD than the non-HFNC group, the timings of the first and of full oral feeding and duration of exposure to oxygen and PMA at discharge from the NICU were comparable between the two groups.

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**Fig. 2.** Distribution of postmenstrual age (PMA) in weeks at A: first oral feeding and at B: full oral feeding. We evaluated the differences between the two groups using the Mann–Whitney U test. PMA: postmenstrual age, HFNC: high-flow nasal cannula, ●: infants in the HFNC group, ■: infants in the non-HFNC group.

**Fig. 3.** Distributions of A: total duration of exposure to oxygen and B: PMA in weeks at the time of hospital discharge. We evaluated the differences between the two groups using the Mann–Whitney U test. PMA: postmenstrual age, HFNC: high-flow nasal cannula, n.s.: not significant, ●: infants in the HFNC group, ■: infants in the non-HFNC group.
Although many previous studies have compared HFNC and nCPAP in preterm VLBWIs in terms of the usefulness of HFNC as a backup in the case of extubation failure and nasal trauma [6–9], few studies have addressed oral feeding [9, 14–19]. Two retrospective cohort studies reported that HFNC are more beneficial in achieving oral feeding than nCPAP in VLBWIs born before 32 weeks PMA [14, 15]. Shetty et al have reported that in infants with bronchopulmonary dysplasia (BPD) who required respiratory support beyond 34 weeks PMA, those supported by nCPAP and subsequently transferred to HFNC achieved full oral feeding before those supported only by nCPAP [14]. Yoon et al reported that there was no difference in respiratory and other outcomes between HFNC and nCPAP groups, but the HFNC group achieved full feeding and regained birth weight sooner [15]. Several other studies, however, revealed no difference between HFNC and nCPAP groups in the feeding ability of preterm VLBWIs. Taken together, compared with nCPAP, the advantage of HFNC in oral feeding of preterm VLBWIs is still controversial because of the differences in study populations and feeding protocols.

Our study differed from previous studies [9, 14–19] in that it compared a HFNC group with a non-HFNC group, not with a nCPAP group, in terms of the feeding ability of preterm VLBWIs. Oral feeding is not introduced during nCPAP in our NICU because it might have an increased risk of nasopharyngeal reflux and tracheal aspiration [20], but Hanin et al reported that infants with BPD who were orally fed during nCPAP could achieve full oral feeding 17 days sooner than those who were not orally fed during nCPAP [21]. Further studies of the oral feeding protocol for infants with CLD are needed in our NICU.

This study also revealed that HFNC prevented prolongation of exposure to oxygen and PMA at discharge from the NICU. Although the HFNC group was more preterm than the non-HFNC group, there was not a significant difference between the two groups in the timing of discharge from the NICU or in achievement of oral feeding. A recent meta-analysis also suggested that oral stimulation shortens hospital stay in preterm VLBWIs [11]. Tsai et al reported that the delay of neonatal oral motor function is closely related to neurodevelopmental outcomes at 6 and 12 months [22].

In this study, the infants did not undergo oral stimulation; fetuses acquire the ability to suckle and swallow from the third trimester, and preterm VLBWIs are assumed to be able to take oral feeding from ≥ 34 weeks PMA [23]. Previous studies have revealed that early oral stimulation therapy could accelerate oral feeding and decrease the time to achieve full oral feeding [11]. As oral feeding development and brain maturation are closely related, it might be preferable to introduce oral feeding in preterm VLBWIs, even if they have CLD. Furthermore, pre-feeding oral stimulation and oral feeding development in preterm VLBWIs in the NICU might be useful as mental support for mothers [24]. Earlier oral feeding by using HFNC could improve the mothers’ mental health and facilitate the mother–infant relationship through early feeding. Further studies are warranted to elucidate the beneficial effects of earlier oral feeding.

This study had several limitations. First, it was a retrospective study with a small sample size. Second, significant differences were recognized between the HFNC and non-HFNC groups in gestational age, body weight, and CLD. Third, we could not evaluate the effect of HFNC on psychomotor development because the subjects did not reach 10 months of age. Recently, Collins et al reported that a different noninvasive respiratory support method (HFNC vs. nCPAP) could differently affect sleep and wake activity in preterm VLBWIs [25]. We plan to examine the psychomotor development of infants in the future.

In conclusion, using HFNC in the introduction of oral feeding in VLBWIs with CLD, who need noninvasive ventilation, is safe and might accelerate the achievement of oral feeding milestones. Further studies are needed to elucidate whether early introduction of oral feeding in infants on HFNC could improve their mental and psychomotor developmental outcomes.

**Conflicts of interest**

The authors report no conflict of interest.

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High Flow Nasal Cannula療法が慢性肺疾患の極低出生体重児の経口哺乳確立に与える影響

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要旨：極低出生体重児における high flow nasal cannula (HFNC) の研究として、人工呼吸器離脱後の呼吸補助作用や呼吸器使用に伴う鼻の創傷について経鼻持続陽圧呼吸 (N-CPAP) と比較検討されてきた。しかし、HFNC 療法が極低出生体重児の経口哺乳へ及ぼす影響に関してはわからていない。今回、対象症例を有する極低出生体重児を対象に HFNC 療法が経口哺乳へ与える影響について後方視的検討した。対象となった 45 症例の慢性肺疾患を有する極低出生体重児中、11 症例が HFNC を使用して経口哺乳が開始され、34 症例が HFNC を使用せず経口哺乳が開始されていた。HFNC 使用群は、HFNC 非使用群と比較すると在胎週数、出生体重共に有意に低値であったが、酸素投与期間および NICU 在院日数には有意差をみとめなかった。また、HFNC 使用群の経口哺乳開始時期の中央値（範囲）は修正週数 35.3 週（33.0 ～ 38.1）vs. 35.5 週（33.7 ～ 42.4）（P=0.91）、経口哺乳確立時期は修正週数 38.6 週（34.4 ～ 42.3）vs. 36.7 週（34.6 ～ 44.4）（P=0.29）であり、HFNC 非使用群と比較して有意な遅れを認めなかった。HFNC 使用群において経口哺乳中の誤嚥性肺炎などの有害事象はなかった。慢性肺疾患の極低出生体重児においても HFNC を使用することにより早期から安全な経口哺乳訓練が可能となり、経口哺乳の確立を安全に促進させる可能性が示唆された。

キーワード：高流量鼻カニュラ酸素療法、経口哺乳、慢性肺疾患、早産児、極低出生体重児。

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