Original Article

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The Effect of Post-extubation Nasal HFOV Support on Extubation Success in Premature Babies in the Neonatal Intensive Care Unit

Mehmet Fatih Deveci*, Halil Aslan**, Mehmet Kilic**, Aydin Bozkaya**, Ihsan Yildirim**

*Harran University Faculty of Medicine, Department of Pediatrics, Division of Neonatology, Sanliurfa, Turkey
**Sanliurfa Harran University Training and Research Hospital, Neonatal Intensive Care Unit, Sanliurfa, Turkey

Abstract

Aim: Currently, it is recommended to use the nasal intermmittent positive pressure ventilation (NIPPV) mode after extubation. The nasal high-frequency oscillator ventilation (NHFOV) mode, which does not require synchronization, is being investigated to be used as a non-invasive ventilation mode. We aimed to compare the effect of NHOFV and NIPPV used after extubation.

Methods: Our study was a randomized controlled study, and according to the power analysis results, 82 patients were included. The study was performed between September 2022 and March 2023. Post-extubation, the patients were randomly assigned to the NHFOV and NIPPV modes. Patients reintubated within the first 72 hours were considered extubation failures. The extubation success rate, demographic and clinical data, and blood gas values of the patients were analyzed.

Results: A total of 82 patients were evaluated. No statistically significant difference was found when the extubation success rate was compared in the NHFOV and NIPPV groups (respectively, 80.5% and 73.2%, p=0.432). The partial carbon dioxide pressure was found to be statistically significantly lower in the NHFOV group [respectively, 44.156±12.067 mmHg and 50.634±11.886 mmHg (p=0.017)].

Conclusion: Nasal high-frequency oscillator ventilation is at least as effective as NIPPV for use after extubation. Normalization of blood gas and fewer side effects are promising for routine use.

Keywords: Nasal intermittent positive-pressure ventilation, non-invasive high-frequency oscillatory ventilation, preterm infant, extubation success

Introduction

Respiratory support is a lifesaving practice for newborns, especially for premature infants. Non-invasive ventilation (NIV) is positive pressure ventilation support, without intubation, provided using various interfaces to patients with adequate respiratory effort. Non-invasive ventilation support plays an important role in the management of respiratory distress in premature infants. Despite NIV support and surfactant therapy, some patients may still require invasive mechanical ventilation (1). Prolonged invasive ventilation increases the risk of morbidity and mortality in these infants (2,3). Therefore, the management of such patients should focus on minimizing intubation and reducing its duration as much as possible (1).

Various NIV strategies have been developed to reduce the need for invasive mechanical ventilation. Providing NIV support to patients after extubation reduces the reintubation rate. Non-invasive ventilation can be applied in various ways such as nasal continuous positive airway pressure (NCPAP), nasal intermittent positive-pressure ventilation (NIPPV), and high-flow nasal cannula. Nasal continuous positive airway pressure has been used successfully for nearly 50 years (4). Recent

Corresponding Author: Mehmet Fatih Deveci, Harran University Faculty of Medicine, Department of Pediatrics, Division of Neonatology, Sanliurfa, Turkey
E-mail: dr-mfd@hotmail.com **ORCID:** orcid.org/0000-0002-3328-4156
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studies have shown the use of NIPPV after extubation reduces reintubation, the need for surfactant, and air leaks compared to NCPAP (5). High-frequency oscillator ventilation (HFOV) is a mode of ventilation that employs tidal volumes less than dead space and is effective in eliminating carbon dioxide by providing constant lung expansion (6). Today, the increase in the successful use of invasive HFOV has led to the consideration of using nasal high-frequency oscillator ventilation (NHFOV). Although there are studies in the literature showing that the use of NHFOV post-extubation is as effective as the NIPPV mode, it is not sufficient to recommend it for routine use (7-10).

In this study, we aimed to investigate the effectiveness of post-extubation NHFOV on extubation success compared to NIPPV. In this way, we hope to decrease the reintubation rates among premature infants and protect them from the harms associated with long-term intubation.

Materials and Methods

Compliance with Ethical Standards

This study was conducted in the Neonatal Intensive Care Unit of Sanliurfa Harran University Training and Research Hospital. Ethical approval from Harran University Clinical Research Ethics Committee was obtained prior to the study (approval no.: HRÜ/22.14.18, date: 25.07.2022).

Study Design and Patients

This randomized controlled study was performed between September 2022 and March 2023. The study was carried out in accordance with the Helsinki Declaration. Infants with a gestational age of 26-34 weeks were included in the study. Infants who were intubated within first hour after birth and remained intubated for at least 12 hours were included in the study. Patients with severe central, cardiac and chromosomal anomalies were not included in the study. Informed consent was obtained from the parents before the study.

Demographic and clinical characteristics of the patients (birth weight, gestational age, gender, mode of delivery, 1st and 5th minute APGAR score, surfactant requirement, postnatal day of extubation) were obtained. Post-extubation, patients were placed on NIV support using NIPPV and NHFOV modes. Extubation patients who were reintubated within 72 hours of NIV support was considered unsuccessful. The nutritional status of the patients was also recorded while under NIV support. During follow-up with NIV, any deterioration in the nutritional plan of the patients due to vomiting, gastric residue, or abdominal distension (reducing the nutritional volume by at least half or skipping 2 consecutive nutrition feeds) was considered feeding intolerance (11). In addition, blood gases taken 1 hour after extubation of the patients were evaluated.

Randomization and Bliding

Infants who met the inclusion criteria and were extubated on nasal respiratory support were randomly divided into two groups. As a randomization method, the "Simple Randomization (or Complete Randomization)", which is known as the assignment of individuals who meet the criteria for participation in the study to the groups with equal chance, completely randomly and regardless of the previous assignment, was used (12). An open-label study design was used (13). Using sealed envelopes for randomization, patients were divided into two groups: NIPPV and NHFOV, according to the nasal respiratory support mode used after extubation.

NIV Protocol

All patients were taken to NIV support with the Leoni Plus ventilator (Löwenstein Medical, Bad Ems, Germany), device, and nasal mask (Medin Medical Innovations GmbH, Olching, Germany). In our clinic, initial NIPPV values are set at positive end-expiratory pressure 5-7 cmH_2O, peak inspiratory pressure 15-20 cmH_2O, frequency 30-40/min, inspiratory time 0.4 sec, and fraction of inspired oxygen (FiO_2) at 0.21-0.50 according to the target oxygen saturation range (90-95%). Initial NHFOV values include: frequency 10-12 Hz, inspiration: expiration ratio 1:1, amplitude 20-30 cmH_2O, pressure mean 8-10 cmH_2O, and FiO_2 is set to 0.21-0.50 according to the target oxygen saturation range (90-95%). In NHFOV mode, we do not expect a visible tremor like in invasive HFOV. The machine sound can be detected while listening to the patients' respiratory sounds. Also, in NIPPV mode, detecting the PEEP by listening to the patient's respiratory sound shows that nasal support has started effectively. In the follow-ups, the settings are changed according to the patient's clinical condition, chest X-ray, and blood gas values. Patients with clinical signs of severe respiratory distress (tachypnea, retraction) on NIV support, patients with the partial carbon dioxide (PCO_2) pressure value above 65 mmHg, patients with a persistent FiO_2 requirement of more than 0.50 to reach the target oxygen saturation level, and patients who experience frequent apnea attacks or need positive pressure ventilation more than twice a day were reintubated.

Statistical Analysis

The method used to determine the sample population of the study is "Systematic Sampling". When Type 1 error amount (alpha) was 0.05, test power (1-beta) was 0.90, effect size was 0.65 (large), and alternative hypothesis (H1) was two-sided, the required minimum sample size to find a statistically significant difference between the NIPPV and NHFOV groups was determined. The study should include a total of 82 individuals, with 41 participants in each group. Sample size calculations

were performed using G*Power version 3.1.9.7 (14). The Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, USA) was used for statistical analysis of the research data. The Shapiro-Wilk test was used to check the conformity of continuous variables with normal distribution. Independent Student's t-test was used for two independent group comparisons of normally distributed variables, and Mann-Whitney U test was used for two independent group comparisons of non-normally distributed variables. Normally distributed continuous data were expressed as mean ± standard deviation, and non-normally distributed continuous data were expressed as median (minimum-maximum). The relationship between categorical variables was tested with chi-square and Fisher's exact analysis. P<0.05 was considered statistically significant.

Results

Our study group, consisting of 82 patients, was all infants who were intubated due to respiratory distress within the first hour after birth. The median gestational age of our patients was 29 weeks (26-33) and the median birth weight was 1265 grams (800-2350). Patients were divided into NIPPV and NHFOV groups, with 41 patients in each group. Both groups had statistically similar characteristics in terms of gestational age, birth weight, gender, mode of delivery, and APGAR scores. Patients were extubated on nasal respiratory support on the median day 2, with a range of 1-15, and postnatal extubation days were statistically similar in both groups. The extubation success rate was 76.8% in our patients extubated to nasal respiratory support. No statistically significant difference was found when the extubation success rate was compared in the NHFOV and NIPPV groups [respectively, 80.5% and 73.2%, (p=0.432)]. Feeding intolerance developed in a total of 9 patients, and no statistical difference was found between the two groups (Table 1).

When the blood gas values taken after extubation were compared between the two groups, the PCO_2 was found to be statistically significantly lower in the NHFOV group [respectively, 44.156±12.067 mmHg and 50.634±11.886 mm/Hg (p=0.017)] (Table 2).

Table 1. Demographic and clinical data of patients

	All patients (n=82)	NIPPV group (n=41)	NHFOV group (n=41)	p-value†
Gestational age week*	29 (26-33)	29 (26-33)	29 (26-33)	0.260
Birth weight g*	1265 (800-2350)	1180 (800-2070)	1400 (830-2350)	0.066
Gender (Female) n (%)	39 (47.6)	19 (46.3)	20 (48.8)	0.825
Mode of delivery (Caesarean) n (%)	73 (89)	36 (87.8)	37 (90.2)	1.000
1st min APGAR score*	6 (2-8)	6 (2-8)	7 (2-8)	0.247
5th min APGAR score*	8 (4-10)	8 (5-10)	8 (4-9)	0.550
Need for surfactant n (%)	57 (69.5)	27 (65.9)	30 (73.2)	0.472
Postnatal day of extubated day*	2 (1-15)	2 (1-15)	2 (1-12)	0.625
Extubation success rate n (%)	63 (76.8)	30 (73.2)	33 (80.5)	0.432
Nutritional intolerance n (%)	9 (11)	6 (14.6)	3 (7.3)	0.482

*Values are given as median (minimum-maximum) and Mann-Whitney U test was used
Categorical variables are given as persentages and chi-square/Fisher's exact test was used
†Results of statistical comparisions betwen NIPPV and NHFOV groups
NIPPV: Nasal intermmittent positive pressure ventilation, NHFOV: Nasal high-frequency oscillator ventilation, min: Minute

Table 2. Blood gas values taken in the first hour after extubation

	All patients (n=82)	NIPPV group (n=41)	NHFOV group (n=41)	p-value†
Ph**	7.309±0.090	7.296±0.091	7.322±0.089	0.185
The partial pressure of carbon dioxide** mmHg	47.395±12.340	50.634±11.886	44.156±12.067	0.017
Bicarbonate** mmol/L	20.172±2.483	20.404±2.441	19.940±2.533	0.399
Base excess** mmol/L	-4.814±2.903	-4.530±2.76	-5.100±3.046	0.377
Lactate*	1.8 (0.5-7)	1.6 (0.5-6.3)	1.90 (0.79-7)	0.138

*Values are given as median (minimum-maximum) and Mann-Whitney U test was used
**Values are given mean ± standard deviation and the Independent Samples t-test was used
†Results of statistical comparisions betwen NIPPV and NHFOV groups
NIPPV: Nasal intermmittent positive pressure ventilation, NHFOV: Nasal high-frequency oscillator ventilation

Discussion

Successful extubation strategies represent an important issue, and are under continuous investigation. Early and successful extubation prevents mortality and many morbidities (1). In our study, we investigated the effect of NHFOV and NIPPV modes used in NIV ventilatory support after extubation on extubation success. We found that NHFOV was at least as effective as NIPPV in the first 72 hours after extubation.

Nasal intermittent positive-pressure ventilation is recognized as the best modality after extubation for successful transition of infants from invasive to non-invasive modes. However, the lack of synchronization may reduce the success of NIV support (6). The idea that NHFOV will be more effective in extubation success is currently being considered. Research on this subject continues. Nasal high-frequency oscillator ventilation can be viewed as a combination of invasive HFOV and NCPAP. It increases the effectiveness of NIV support by reaching higher pressure values due to overlapping vibrations of the gas. It is also an important advantage that it does not require synchronization (15,16). In a study comparing NHFOV and NCPAP, NHFOV was proven to have better extubation success than NCPAP (8). A recent meta-analysis published in 2023 found that NHFOV reduced intubation and reintubation rates in premature infants compared to NCPAP. Additionally, it did not lead to an increase in complications potentially associated with NIV (17). In a study of infants with RDS born below 32 weeks, the NIPPV and NHFOV modes were found to be more appropriate for post-extubation use than NCPAP (18). Seth et al. (10) found that there was no difference between NHFOV and NIPPV modes used post-extubation in terms of extubation failure in their study. A meta-analysis published in 2023 included eight studies comparing NIPPV and NHFOV involving 1603 patients. Nasal high-frequency oscillator ventilation was found to reduce reintubation rates without increasing adverse outcomes (19). The meta-analysis, which included 23 studies involving 2331 newborns, determined that the NHFOV mode was the most effective option post-extubation (20). In our patients, we found that the extubation success of the NHFOV group was proportionally higher, although there was no statistical difference.

Carbon dioxide level is an indicator of adequate ventilation. In intensive care patients, blood gas carbon dioxide levels are closely monitored and the patient's ventilation support is adjusted. Hypercarbia is an important cause of reintubation. An advantage over NIPPV in NHFOV mode is that it is more efficient at eliminating carbon dioxide. Studies have found that NHFOV is more effective in reducing pCO_2 and normalizing blood gas levels (16,18,21). In our study group, we found that pCO_2 was lower in the NHFOV group, which is consistent with findings reported in the literature. Nasal high-frequency oscillator ventilation is not routinely used in clinics. For patients who need reintubation due to hypercarbia while in NIPPV mode, trying NHFOV mode before reintubation may help avoid unnecessary intubation.

Complications such as pulmonary air leaks and feeding intolerance may occur with NIV support (15,22). An experimental study involving 8 lambs found that the NHFOV mode significantly inhibited gastroesophageal reflux (23). In a study of 81 infants with RDS, the NHFOV mode was shown to significantly reduce the need for invasive mechanical ventilation compared to NCPAP, without increasing the incidence of side effects (24). During NIV support, abdominal distension due to the passage of gas into the gastrointestinal system may cause feeding intolerance (22). In our study, pulmonary air leakage did not develop in any of our patients. However, feeding intolerance occurred in nine patients, with a lower incidence observed in the NHFOV group, though the difference was not statistically significant. On the other hand, all our patients with feeding intolerance were immature infants, weighing less than 1000 g. Although NHFOV appeared to be safer in terms of nutritional intolerance, it was not possible to directly connect the experienced nutritional intolerance to NIV support.

Study Limitations

Our study was limited due to being single-center and having a limited number of cases. In addition, our patients were only followed for the first 72 hours after extubation, and the lack of long-term results is a limitation of our study. Despite these limitations, It also has strengths such as being a randomized controlled trial and being a current and important issue for premature babies.

Conclusion

We found that NHFOV was at least as effective as NIPPV in NIV support in the first 72 hours after extubation. Nasal high-frequency oscillator ventilation seems more promising than NIPPV regarding side effects and blood gas values. The carbon dioxide levels of patients placed on NHFOV post-extubation were lower than in patients monitored on NIPPV. It can be speculated that patients monitored on NHFOV mode may need closer carbon dioxide level monitoring. More randomized controlled studies are needed on this subject.

Ethics

Ethics Committee Approval: Ethical approval from Harran University Clinical Research Ethics Committee was obtained prior to the study (approval no.: HRÜ/22.14.18, date: 25.07.2022).

Informed Consent: Informed consent was obtained from the parents before the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.F.D., H.A., M.K., A.B., I.Y., Concept: M.F.D., H.A., Design: M.F.D., H.A., Data Collection or Processing: M.F.D., H.A., M.K., A.B., I.Y., Analysis or Interpretation: M.F.D., Literature Search: M.F.D., Writing: M.F.D.

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