

Safety and Long Term Outcomes with High Flow Nasal Cannula Therapy in Neonatology: A Large Retrospective Cohort Study

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Abstract

Objective: High flow nasal cannula therapy (HFT) has been shown to be similar to nasal continuous positive airway pressure (nCPAP) in neonates with respect to avoiding intubation. The objective of the current study is to determine if there are trends for adverse safety and long-term respiratory outcomes in very low birth weight infants (<1500 g) from centers using HFT as their primary mode of non-invasive respiratory support compared to data from the largest neonatal outcomes database (Vermont Oxford Network; VON).

Methods: A multicenter, retrospective analysis of pulmonary outcomes data was performed for the calendar years 2009, 2010 and 2011. Performance of five HFT centers was compared with population outcomes from the VON database. The five HFT centers routinely use flow rates between 4-8 L/min as described by the mechanistic literature. Weighted average percentages from the five HFT centers were calculated, along with the 95% confidence intervals (CI) to allow for comparison to the VON means.

Results: Patient characteristics between the HFT centers and the VON were not different in any meaningful way, despite the HFT having a greater percentage of smaller infants. The average VON center primarily used nCPAP (69% of all infants) whereas the HFT centers primarily used HFT (73%). A lesser percentage of VLBW infants in the HFT cohort experienced mortality and nosocomial infection. Compared to VON data, an appreciably lesser percent of the HFT cohort were receiving oxygen at 36 weeks and less went home on oxygen.

Conclusions: Considering there was no trend for adverse events, and there was a trend for better outcomes pertaining to long-term oxygen use, these data support claims of safety for HFT as a routine respiratory management strategy in the NICU.

Keywords: High flow therapy; High flow nasal cannula; Work of breathing; Respiratory Dead space; Ventilatory efficiency; Oxygen therapy; Neonatal respiratory distress

Introduction

In recent years there has been a marked increase in the use of nasal cannulae for the delivery of high flow humidified respiratory gas to neonatal patients. This rise in clinical acceptance has furthered the demand for data on long-term clinical outcomes, which is dependent on establishing uniformity in high flow nasal cannula therapy (HFNC) definition and implementation. HFNC is loosely defined as nasal cannula therapy with a gas flow that exceeds conventional cannula flow rates, which in the neonatal population is associated with a flow greater than 1 or 2 L/min, depending on the source [1]. Mechanistic research, which underscores the translational approach to defining HFNC, has pointed to the advantages of using higher flow rates to accomplish specific physiologic objectives in order to optimize therapeutic effect [2,3].

In 2003 the concept of HFNC was adapted to the neonatal intensive care unit (NICU) application with the use of heated humidifiers that would condition the gas to avoid damaging the nasal tissues [4]. The therapy was viewed primarily as an alternative means of providing nasal continuous positive airway pressure therapy (nCPAP), albeit with a patient interface that is easier to manage than a sealed nCPAP system. Since then, translational research has demonstrated that HFNC

is distinct from nCPAP, and that the primary mechanism of action is not a function of pressure [2]. Moreover, if administered with flow rates and patient interface designs that avert pressure and focus on dead space reduction, HFNC can be optimized. This approach to the use of HFNC is termed High Flow Therapy (HFT).

Recently, three randomized, controlled studies have reported on clinically important short-term outcomes associated with HFNC [5-7]. These three trials showed that HFNC appears to have similar efficacy and safety to nCPAP when applied immediately post-extubation. Moreover, another recent study by Kugelman and colleagues showed equivalency in short-term outcomes between HFNC and nasal intermittent positive

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pressure ventilation [8]. In the present study, we sought to establish a more long-range comparison of clinical outcomes between HFT and nCPAP. While not a surrogate for a randomized controlled trial for efficacy, these retrospective data evaluate long-term pulmonary outcomes on over 1,300 HFT patients, thus identifying trends for safety and the impact of HFT on critical pulmonary parameters under current clinical practice.

Methods

The current study model compares three calendar years of pulmonary outcomes data through patient discharge from five centers, which have incorporated HFT as standard non-invasive respiratory support, with population outcomes data from the Vermont Oxford Network (VON) neonatal database [9]. The authors of the present paper include clinicians from the five neonatal centers that use HFT extensively in place of nCPAP.

The overall outcomes from these HFT centers in the very low birth weight category (VLBW; <1500 g) were compared to the VON averages over the years of 2009, 2010, and 2011. At the time the analysis was run, 2011 was the last full year of data available from VON. The subsequent addition of 2012 data was not considered because of a potential rise in the use of HFT in the VON cohort secondary to recent trials showing short-term efficacy. The HFT centers providing data for comparison to VON were: Banner Estrella, Phoenix, AZ; Baptist Hospital, Nashville, TN; Oxford University Hospital, Oxford, UK; Saint Barnabas Medical Center, Livingston, NJ; UMass Memorial, Worcester, MA.

Definition of High Flow Therapy

Based on mechanistic literature, HFT is defined here as a specific approach to HFNC where respiratory gas is delivered through a nasal cannula at flow rates that exceed a patient's flow demand during inhalation and are sufficient to purge the extrathoracic dead space during exhalation. HFT was administered using similar protocols as well as similar equipment (Precision Flow, Vapotherm, Inc, Exeter, NH) across all five sites. Cannula flow rates needed to accomplish these objectives typically begin at greater than 3 L/min [10], and centers represented in this paper as HFT centers routinely use between 3 L/min and 8 L/min, with flow rates typically between 4 L/min and 6 L/min.

In HFT centers, HFT was used in place of nCPAP and started on infants who were experiencing respiratory distress and not deemed to require immediate mechanical ventilation. The decision to start HFT was based on the same clinical criteria as are conventionally used when initiating nCPAP. HFT was also used as the mode for non-invasive respiratory support immediately following extubation. Infants in all birth weight categories were treated using the same general range of flow rates as described above, which was titrated to clinical effect. The rationale was that flow rate requirements necessary to purge the nasopharyngeal cavity in the neonate are more a function of anatomy and breathing pattern than body size.

Data Analysis

The pulmonary outcome parameters queried for this analysis were incidences of mortality, pneumothorax, nosocomial infection, oxygen use (28 d, 36 wks and at home), retinopathy of prematurity (ROP) and intraventricular hemorrhage. Hospital length of stay was also queried. The data collection and this specific comparison were approved by the Institutional Review Boards for the protection of human subjects at each institution, and the comparison to the VON means was allowed by permission of the VON.

With the exception of mean weight values and total hospital stay, data are presented as percentages of the total enrollment. For comparison, the weighted average percentage from the five HFT centers was calculated along with the 95% confidence intervals (CI). Odd ratios (OR) relative to an association with HFT were calculated for respiratory outcome parameters based on the percentages from each group. Without variance data for VON values, we cannot make decisions of statistical significance, but we can evaluate trends and determine whether the VON values, taken to represent the population, are within the CI for the HFT centers. Thus, the data are amenable to testing the null hypothesis that HFT results in more adverse events and less positive outcomes, rejecting this null if HFT centers trended toward better performance. The data from this comparison are presented as totaled across all three years; the trends seen in the totals were consistent across years.

Results

Data from the HFT centers represent combined VLBW admissions of 446 in 2009, 429 in 2010 and 488 in 2011, totaling 1,363 VLBW infants. The VON database consisted 58,661 VLBW admissions in 2009, 57,992 in 2010 and 59,946 in 2011, totaling 176,599 VLBW babies.

Patient Characteristics

The baseline characteristics of the study population are presented in Tables 1 and 2. The patient populations between the HFT centers and the VON are not different in any meaningful way. The proportion of babies who are classified as "in born" is higher in the HFT centers as compared to the VON data, where the HFT centers mean is 93% (95% CI=90.3%-95.2%) and the VON mean is 85.9%. This difference possibly contributed to the trend for a lower birth weight patient population in the HFT centers. Table 2 shows mean birth weights and weight at initial disposition by year, and Figure 1 shows the percentage distribution

Characteristic	5 HFT Centers x/n (%) (LCL, UCL) ^a	VON Database (%)
In born	1267/1363 (93.0) (91.5, 94.3)	86.2
Gender (male)	719/1363 (52.8) (50.1, 55.4)	51.0
Race		
Caucasian	756/1363 (55.5) (52.8, 58.1)	51.0
African American	338/1363 (24.8) (22.5, 27.2)	24.8
Hispanic	171/1363 (12.5) (10.8, 14.4)	16.4
Asian	92/1363 (6.8) (5.5, 8.2)	5.3
Native American	2/1363 (0.1) (0.0, 0.5)	0.6
Other	4/1363 (0.3) (0.1, 0.8)	2.0
Birth weight (g) ^b		
<501	55/1360 (4.0) (3.1, 5.2)	1.4
501-750	275/1360 (20.2) (18.1, 22.5)	18.4
751-1000	322/1360 (23.7) (21.4, 26.0)	22.6
1001-1250	340/1360 (25.0) (22.7, 27.4)	25.4
1251-2500	368/1360 (27.1) (24.7, 29.5)	32.3
Gestational age (weeks) ^b		
<24	83/1363 (6.1) (4.9, 7.5)	5.6
24-26	390/1363 (28.6) (26.2, 31.1)	23.8
27-29	486/1363 (35.7) (33.1, 38.3)	36.6
30-32	294/1363 (21.6) (19.4, 23.9)	26.7
>32	110/1363 (8.1) (6.7, 9.6)	7.4
Maternal hypertension	361/1363 (26.5) (24.2, 28.9)	28.0
Chorioamnionitis	150/1363 (11.0) (9.4, 12.8)	12.6
Antenatal Steroids	1154/1363 (84.7) (82.6, 86.5)	77.9
Prenatal care (yes)	1316/1363 (96.6) (95.4, 97.5)	95.5

HFT: High flow therapy; LCL: Lower confidence limit; n: population; UCL: Upper confidence limit; VON: Vermont Oxford Network; x: number of patients.

^aExact 95% binomial confidence limits.

^bBirth weight and gestational age were not reported for 3 infants.

Table 1: Population characteristics of very low birth weight newborns for 2009-2011.

Year/Group	Mean Birth Weight (g)	Weight (g) at Initial Disposition
2009		
HFT centers	1005	2200
VON database	1047	2221
2010		
HFT centers	1024	2247
VON database	1048	2245
2011		
HFT centers	1022	2168
VON database	1055	2255

HFT: High flow therapy; VON: Vermont Oxford Network.

Table 2: Mean birth weight distribution by year.

Intervention	5 HFT Centers x/n (%) (LCL, UCL) ^a	VON Database (%)
Use of surfactant	805/1363 (59.1) (56.4, 61.7)	62.4
nCPAP	413/1363 (30.3) (27.9, 32.8)	68.6
HFNC	999/1363 (73.3) (70.9, 75.6)	53.0 ^b
CMV	798/1363 (58.5) (55.9, 61.2)	64.6

CMV: Conventional mechanical ventilation; HFNC: High flow nasal cannula; HFT: High flow therapy; LCL: Lower confidence limit; n: population; nCPAP: nasal continuous positive airway pressure; UCL: Upper confidence limit; VON: Vermont Oxford Network; x: number of patients.

^aExact 95% binomial confidence limits.

^bNote that high flow nasal cannula therapy is the VON definition (cannula flow rate above 1 L/min), so much of the HFNC use in the VON group is not how we define HFT (flow rates between 3 L/min and 8 L/min, commonly in the 4 L/min to 6 L/min range).

Table 3: Comparison of interventions in the 5 HFT study centers and the VON database from 2009-2011.

across birth weight categories. The HFT centers have a greater percentage of smaller infants and a lesser percentage of larger ones, which would likely present a greater clinical management challenge.

Respiratory Management Strategies

Use of respiratory interventions was assessed and is reported in Table 3. We evaluated the use of four therapies that are directly related to respiratory treatment: nCPAP, HFT (HFNC in the case of VON data), conventional mechanical ventilation (CMV), and surfactant use. Data regarding use of nCPAP, HFNC/HFT, and CMV are presented in Figure 2. There is a clear contrast between the average VON center, which primarily used nCPAP (69% of VLBW infants), and the five HFT centers, which had reduced use of nCPAP (30% of the VLBW infants compared to 73% on HFT). Ventilator use may also have been reduced and there was an indication that there might have been less surfactant use in the HFT centers (HFT=59.1%, CI 56.4% to 61.7%; VON=62.4%).

Respiratory Related Outcomes

Data on respiratory related outcomes are presented in Table 4. A lower percentage of VLBW infants in the HFT group experienced mortality and nosocomial infection compared to VON (OR=0.88). The comparison for the rate of pneumothorax showed 4.8% (95% CI 3.8% to 6.1%) in the HFT group to 4.4% in the VON group; OR=1.09 and well within the 95% CI. There were interesting findings with respect to oxygen usage. Figure 3 shows that compared to the VON percentages, a slightly greater percentage of HFT group infants were on oxygen at 28 days (OR=1.08 with VON outside the 95% CI for HFT), but then an appreciably lesser percent of the HFT group infants were on oxygen at 36 weeks (OR=0.80) and less went home on oxygen (OR=0.50). This

trend is again reflected in the incidence of retinopathy of prematurity (ROP), where a lower percentage of HFT infants underwent surgery for ROP (OR=0.69), and as seen in Figure 4 there was a shift in ROP grade distribution demonstrating a greater percentage of HFT group infants had no ROP (OR=1.19).

Discussion

The current study explores long-term outcomes between centers that use HFT as the primary means of non-invasive ventilatory support, compared to the mean performance of centers in the VON database, where nCPAP is the primary mode of non-invasive support and HFNC is defined as flows greater than 1 L/min. These data from large patient cohorts can only be used cautiously to infer differences between groups, but clearly demonstrate no increased risk for short or long term adverse pulmonary outcomes associated with HFT compared to conventional standard of care. The mean data from the VON database are outside of

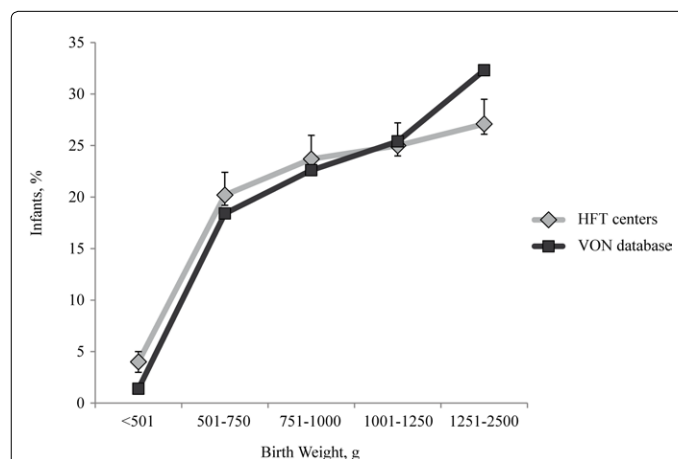


Figure 1: Percentage Distribution across Birth Weight Categories. HFT centers appear to have a greater percentage of smaller infants and a lesser percentage of larger ones. Error bars represent 95% confidence interval for 5 HFT centers.

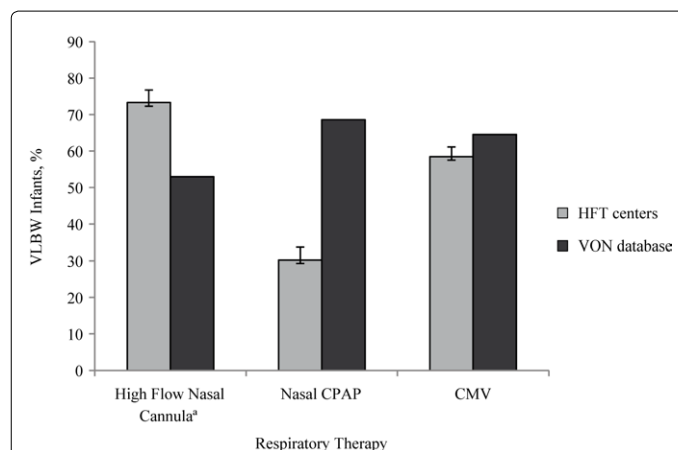


Figure 2: Percent VLBW Infants Supported on each Respiratory Therapy during their Stay. High flow nasal cannula was used more frequently in the High Flow Therapy (HFT) centers compared to the typical center in the Vermont Oxford Network (VON) database; however, the use of high flow nasal cannula in the VON database did not necessarily meet the definition of HFT. There is a contrast between the use of nasal continuous positive airway pressure (CPAP) for the VON database and HFT centers, where HFT centers were replacing nasal CPAP with HFT. Ventilator use may also have been reduced within the HFT centers. Error bars represent 95% confidence interval for five HFT centers.

the 95% confidence intervals around the HFT center means for oxygen use, with the VON data showing a greater incidence of oxygen use at the 36 week time point as well as oxygen use at home. The mechanistic understanding of HFT may support this trend for reduced long-term oxygen use [3].

There are a couple of important caveats related to the data presented in Table 3 and Figure 2. Firstly, the use of HFNC in the VON group is based on the VON definition, which uses a cannula flow rate above 1 L/min. Because of this, the report that 53% of the VON VLBW infants were supported on HFT (as compared to the 73% in the HFT centers) is, by our definition of HFT, a dramatic overestimation. This presumption

Outcome	5 HFT Centers x/n (%) (LCL, UCL) ^a	VON Database (%)	Odds Ratio
Mortality	163/1363 (12.0) (10.3, 13.8)	13.6	0.88
Pneumothorax	66/1363 (4.8) (3.8, 6.1)	4.4	1.09
Nosocomial infection	202/1363 (14.8) (13.0, 16.8)	15.1	0.98
O2 at 28 days	693/1363 (50.8) (48.1, 53.5)	47.0	1.08
O2 at 36 weeks	331/1363 (24.3) (22.0, 26.7)	30.4	0.80
O2 at home	85/1363 (6.2) (5.0, 7.7)	12.5	0.50
ROP stage			
0	1113/1363 (81.7) (79.5, 83.7)	68.8	1.19
1	101/1363 (7.4) (6.1, 8.9)	14.4	0.51
2	115/1363 (8.4) (7.0, 10.0)	10.6	0.79
3	31/1363 (2.3) (1.6, 3.2)	6.0	.038
4	3/1363 (0.2) (0.0, 0.6)	0.2	1.00
5	0/1363 (0.0) (0.0, 0.3)	0.1	0.00
ROP surgery	30/1363 (2.2) (1.5, 3.1)	3.2	0.69
IVH grade			
0	1054/1363 (77.3) (75.0, 79.5)	75.4	1.03
1	136/1363 (10.0) (8.4, 11.7)	10.8	0.93
2	102/1363 (7.5) (6.1, 9.0)	5.6	1.34
3	24/1363 (1.8) (1.1, 2.6)	3.5	0.51
4	47/1363 (3.4) (2.5, 4.6)	4.7	0.72
Mean days in hospital	62.0	60.7	

HFT: High flow therapy; IVH: Intraventricular hemorrhage; LCL: Lower confidence limit; n: population; ROP: Retinopathy of prematurity; UCL: Upper confidence limit; VON: Vermont Oxford Network; x: number of patients.

^aExact 95% binomial confidence limits.

Table 4: Respiratory related outcomes for the 5 HFT centers compared to the VON database for 2009-2011.

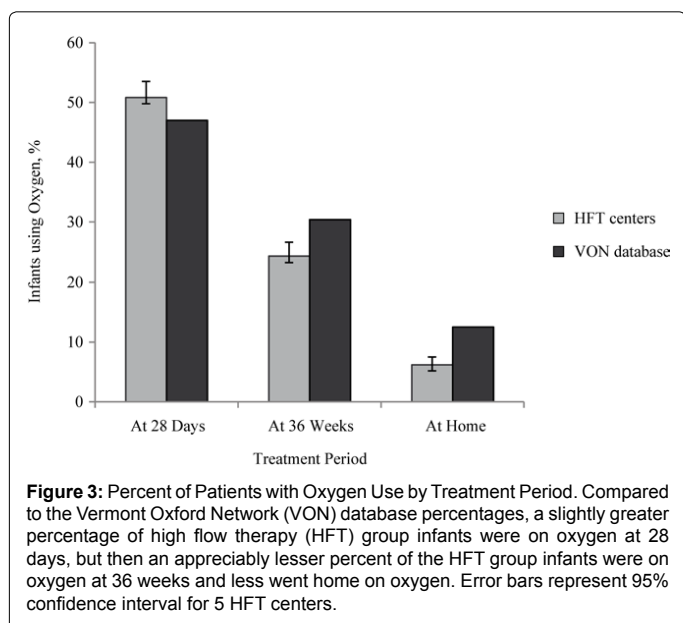


Figure 3: Percent of Patients with Oxygen Use by Treatment Period. Compared to the Vermont Oxford Network (VON) database percentages, a slightly greater percentage of high flow therapy (HFT) group infants were on oxygen at 28 days, but then an appreciably lesser percent of the HFT group infants were on oxygen at 36 weeks and less went home on oxygen. Error bars represent 95% confidence interval for 5 HFT centers.

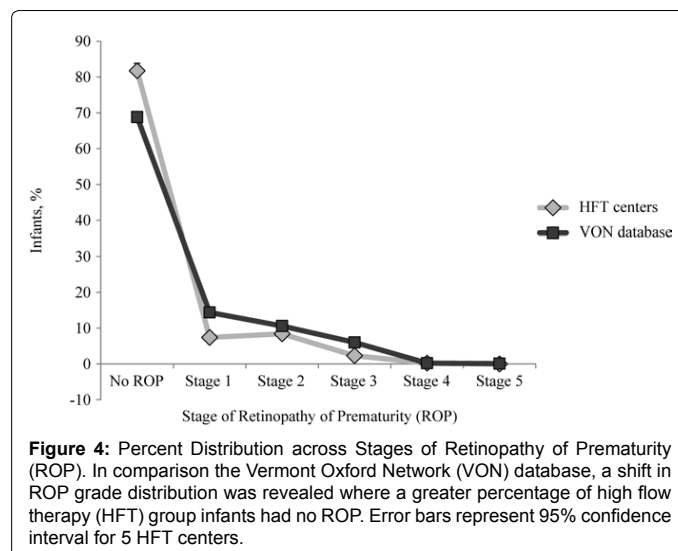


Figure 4: Percent Distribution across Stages of Retinopathy of Prematurity (ROP). In comparison the Vermont Oxford Network (VON) database, a shift in ROP grade distribution was revealed where a greater percentage of high flow therapy (HFT) group infants had no ROP. Error bars represent 95% confidence interval for 5 HFT centers.

is based on communications with our colleagues, which indicated that many centers are using lower flow rates (1.5 or 2 L/min) as a step-down from nCPAP and reporting this, appropriately, as HFNC use. Secondly, some of the use of nCPAP reported by the HFT centers was related to therapy used on arrival or at disposition from the NICU, and therefore cannot be relied on as a management paradigm; thus, the use of nCPAP in the HFT group (30%) is also an overestimation.

The HFT centers in this study routinely used greater flow rates than what is defined as HFNC by VON. This decision is based on clinical experience and on the mechanistic rationale that HFT purges anatomical dead space. CPAP and HFNC/HFT differ in the mode of delivery and ultimate mechanisms of action [2,3], contributing to possible differences in the susceptibility of the patients to coincidental sequelae. Comparing the relative incidence of untoward outcomes for CPAP and HFNC/HFT, the underlying therapy itself should be considered. CPAP systems are specifically designed to be a closed system, in conjunction with an infant's respiratory tract. The proposed mechanisms of action for CPAP are complex and multifactorial, but include the concept that pressure is able to recruit lung alveoli by increasing functional residual capacity, thus improving compliance so that greater minute ventilation (VE) can be achieved to account for the necessary alveolar ventilation (VA) [11]. From a mechanical perspective, CPAP supports spontaneous breathing by making it less taxing to stretch the lung and by minimizing atelectrauma during lung stretch. HFT, on the other hand, is aimed at achieving VA with lesser VE, so as to reduce the necessary lung stretch. Nonetheless, the accompanying humidification and mild pressure effects with HFT would attenuate atelectrauma as well [12,13].

To prevent the coinciding nasal pressure from reaching levels that would require monitoring, and instead provide adequate anatomic release, literature dictates that cannulae should not occlude more than 50% of the diameter of the nares. This recommendation is based on the work of Locke and colleagues [14], who showed that nasal prongs with an outside diameter no more than 50% of the internal diameter of the nares did not result in distending pressure during low-flow O2 therapy. Cannulae meeting these requirements were used at all five of the HFT sites in this study. Care must be made in extending the results to sites employing alternative nasal cannulae or procedures. Care must be taken with HFT to adjust flows to sufficient levels to meet patient demands. Procedures in place in all five HFT sites provided rationale and guidance to the selection of adequate flow rates.

The range of flow rates to be used with infants is generally accepted to be between 1 and 8 L/min [10]. From a physiological perspective, although infants have a very small tidal volume (VT), in the range of 4 to 6 mL/kg, their respiratory rates are quite high. Respiratory rates in sick infants can approach 100 breaths per minute, creating very high inspiratory flow rates relative to VE. Another consideration with infants, which pertains to the mechanism of dead space purge, is the relative size of the anatomical reservoir, which consists of the extrathoracic dead space volume of the nasal, oral, and pharyngeal cavities. Infants have a much larger anatomical reservoir relative to older children and adults. Numa and Newth showed that while small infants have an extrathoracic dead space volume of around 2.3 mL/kg, this value drops to approximately 0.8 mL/kg in children over 6 years of age, and maintains this level into adulthood [15]. Therefore, as compared to an adult, an infant may need greater relative flow rates to realize the full benefits of purging the anatomical reservoir in the window of opportunity between breaths (flow rates that go beyond simply meeting inspiratory demand). This three-fold greater anatomical reservoir volume in small infants translates to dead space making up a much greater fraction of their tidal volume as compared to larger children and adults.

Limitations

A limitation of this paper is that the data comparison is retrospective and absent a parallel control group. Patients from four of the five HFT centers are also included within the VON database. However, the very large sample sizes across three years of use, and the distinct difference in therapeutic approach between the groups, presents a powerful and practical picture for the impact of adoption of HFT on respiratory outcomes compared to accepted standard outcomes represented in the VON database. Moreover, the data comparison included the years before 2012 when there is a presumed inflection point in the routine use of higher flow rates in HFNC secondary to recent trials of short-term efficacy.

The data analyses could not derive statistical conclusions because there is no variance data from the VON database. However, the 95% CI around the HFT centers' data, in conjunction with the presentation of OR, provide some perspective as to the degree of difference. The trends can at least rule out the possibility of a rise in adverse events associated with HFT use.

Conclusion

Ten years of cumulative experience with use of HFT in neonatology affords us the opportunity to look back over data from a large number of infants to identify trends for positive and negative outcomes associated with HFT, namely the use of higher flow rates (>2 L/min) with these smaller infants. Although the analysis presented here is not a surrogate for a prospective trial of efficacy, there was no trend for adverse events, and there was a trend for better outcomes pertaining to long-term oxygen use. Therefore, these results support claims of safety for HFT as a routine respiratory management strategy in the NICU.

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