Irish Medical Journal
Established 1867

Issue: Ir Med J; Vol 112; No. 8; P985

High-flow Nasal Cannulae, Bronchopulmonary Dysplasia and Retinopathy of Prematurity

L.I. Healy[1], P. Corcoran[2], B.P. Murphy[1,3]

1. Cork University Maternity Hospital, Cork City, Ireland
2. Department of Obstetrics and Gynaecology, School of Medicine, University College Cork, Ireland
3. Department of Paediatrics and Child Health, University College Cork, Ireland

Abstract

Aims
To determine if HFNC use was associated with changes in incidence of BPD and ROP.

Methods
This retrospective study examined premature infants (<30 weeks GA or <1500g) in a tertiary neonatal unit from 2010-2016. Patients were compared before and after introduction of HFNC. Further analysis of high-risk infants (<28 weeks GA or <750g or ventilated) compared those who received HFNC to those who did not across the whole period. Primary outcomes were incidence of BPD and ROP requiring surgery.

Results
Incidence of BPD rose following the introduction of HFNC (82/232 (35.3%) after vs 33/251 (13.1%) before, p<0.001). On multivariate analysis, the chance of developing BPD after HFNC introduction remained higher (OR 4.353, 95% CI 2.546-7.443). More infants received surgery for ROP following HFNC introduction (0/214 vs 11/205 (5.4%), p=<0.001). In the second analysis, the rate of BPD was higher in those who received HFNC (90/132 (68.1%) vs 33/153 (21.6%), p<0.001). Receiving HFNC demonstrated higher chance of BPD in multivariate analysis (OR 7.802, 95% CI 4.223-14.423). Rate of ROP surgery was higher in those who received HFNC (0/153 vs 13/134 (9.7%), p<0.001).

Conclusions
In this study, use of HFNC was associated with significantly increased risk of adverse outcomes.

Introduction

High-flow nasal cannulae (HFNC) as respiratory support have been increasingly adopted in neonatal units due to benefits including reduced nasal trauma, being less invasive, allowing teat-feeding and involving parents in infant-cares, when compared to nasal continuous positive airway pressure (CPAP)[1].

In our Neonatal Unit, HFNC are used as a weaning tool from CPAP in premature very low birth weight (VLBW) infants. Randomised controlled trials (RCT) comparing HFNC with CPAP in this context have reported contradictory results.

Soonsowad et al showed that weaning from CPAP via HFNC, versus continuing CPAP and weaning directly to air, lead to no difference in time to wean from respiratory support, rates of BPD or rates of severe ROP (≥stage 3 ROP)[2]. Two other RCTs published on this topic yield conflicting results with one showing infants receiving HFNC had a longer duration of respiratory support[3], and the other reporting decreased length of total oxygen therapy associated with HFNC use[4]. Observational studies also show inconsistent results regarding respiratory outcomes and ROP. While increased rates of bronchopulmonary dysplasia (BPD) and/or longer duration of respiratory support are associated with HFNC, there are conflicting associations between HFNC use and rates of ROP[5-8.]
This study explores the relationship between introduction of HFNC as a means of weaning VLBW infants from respiratory support and rates of BPD, ROP and length of stay in a tertiary neonatal unit.

Methods

This retrospective review in a single tertiary NICU compared outcomes before and after the introduction of HFNC as a means of weaning infants off CPAP. All patients admitted to the unit were eligible for inclusion if their birthweight was less than 1500g or their gestational age (GA) less than 30 weeks, they did not have significant congenital malformation and they did not die in within 12 hours of admission. Data were extracted from an existing database for the years 2010-2016, inclusive. Patients were split into two epochs; before (2010-2012) and after the introduction of HFNC (2014-2016), with 2013 being disregarded as an implementation phase. For additional analyses, we defined a priori a subset of patients considered to be 'eligible' for HFNC (defined as babies with GA<28 weeks, birthweight <750g, ventilated or received surfactant and did not die before discharge). Within this subset of patients, those infants who were supported with HFNC were compared to those who did not receive HFNC support.
The primary outcomes were BPD (*defined as oxygen dependence at 36 weeks CGA*) and severe ROP requiring surgical treatment (laser photocoagulation, anti-VEGF treatments not included in analysis as only introduced 2011). Secondary outcomes included length of stay, any stage of ROP (see below for definitions) and pneumothorax (if seen on chest X-Ray).

HFNC were used as a tool to wean infants from CPAP when greater than 2 weeks of age and stable on CPAP according to specific criteria (PEEP ≤5cm, Fi02≤30%, pH ≥7.25 and no significant apneas). The starting flow was 5-6L/min, increased or decreased in increments of 1L/min.
HFNC were introduced in late 2013 (used on one patient only in 2012), with consistent use from 2014. No other respiratory support guidelines changed during this period. Use of post-natal steroids for ventilator weaning and in surfactant delivery by insure (intubate-surfactant-extubate to CPAP) method[9,10] increased, in line with international trends.

Screening criteria and thresholds for treatment of ROP were based upon UK Retinopathy of Prematurity Guideline[11]. Screening is carried out in house, with treatment provided elsewhere. The ophthalmologist providing screening changed in mid-2014, however neither the indications for treatment, nor the single Ophthalmology surgeon providing treatment changed during the study period.

Use of ibuprofen is included in the regression analysis. During the study period ibuprofen was first-line pharmacotherapy for patent ductus arteriosus (PDA). PDA are confirmed and assessed for haemodynamic significance by echocardiography prior to treatment. Early-onset neonatal sepsis is defined as isolation of a bacterial pathogen recovered from blood and/or cerebrospinal fluid culture in the first three days of life.

Data were analysed in SPSS statistics[12]. Normally distributed data were analysed using an unpaired two-tailed t-test. Non-normally distributed data were analysed using Mann-Whitney U-test. Chi-squared Pearson co-efficient was used for categorical data. Following univariate analysis, multivariate binary logistic regression was performed. Linear data were transformed into categorical data for regression analysis. Factors selected for inclusion in the regression analysis: smaller gestation (less than 28 weeks in the first analysis and less than 26 weeks in the subgroup analysis), birthweight <750g, presence of early onset sepsis, a 5 minute Apgar ≤5, having being ventilated and having received ibuprofen were chosen based on evidence suggesting a significant link with BPD[13–15], and on baseline differences in our data.
This study was approved by Clinical Research Ethics Committee, University College Cork.

Results

Patients and follow-up

There were 573 eligible patients born during the period. Data regarding mortality were missing for two patients. When patients were discharged home or transferred to another facility for nursery care without oxygen before 36 weeks CGA, they were defined as not having BPD. When discharged to another facility before 36 weeks CGA and still receiving oxygen, their data was excluded from BPD calculations. Data regarding ROP stage are included for all patients who had at least one ROP screen performed before discharge. Any other missing data were excluded from calculations.

Pre- and post-HFNC group analysis

There were 256 patients in the pre-HFNC (2010-2012) group and 238 patients in the post-HFNC (2014-2016) group. All had GA<30 weeks or birthweight<1500g. Baseline characteristics differed significantly with respect to higher use of post-natal steroids (9.7% vs 1.2%, p<0.001) and surfactant (59.7% vs 46.9% p=0.004) in the post-HFNC period. More in the post-HFNC were male (55% vs 46.1%, p=0.048), received CPAP treatment (87.8% vs 80.9%, p=0.034) and there was a lower proportion of babies with a 5 minute Apgar>5 (84.9% vs 88.7%, p=0.01). There were no other significant differences between the two groups in baseline statistics (see Table 1).

Table 1: Baseline characteristics of comparison of groups pre (2010-2012) and post (2014-2016) introduction of high-flow nasal cannula.

	2010-2012 (n=256)	2014-2016 (n=238)	Sig
Birthweight ○	1104g (±273g)	1083g (±320)	0.437✦
Gestation ○	29^{+1} weeks ($\pm2^{+5}$)	28^{+6} weeks ($\pm2^{+6}$)	0.18 ✦
Male	118/256 (46.1%)	131/238 (55%)	0.048 †
Multiple birth	103/256 (40.1%)	91/238 (38.2%)	0.649 †
Antenatal Steroids	227/256 (88.7%)	215/236 (91.1%)	0.373 †
5 minute Apgar >5	236/256 (92.2%)	202/238 (84.9%)	0.010 †
Early onset sepsis	4/256 (1.6%)	7/238 (2.9%)	0.299 †
Received CPAP	207/256 (80.9%)	209/238 (87.8%)	0.034 †
Ventilated	127/256 (49.6%)	131/238 (55%)	0.227 †
Surfactant	120/256 (46.9%)	142/238 (59.7%)	0.004 †
Post-natal steroids	3/256 (1.2%)	23/238 (9.7%)	<0.001 †
○=mean±SD; ✦=t-test; †=chi-squared			

The rate of BPD was significantly higher in the post-HFNC group (35.3% vs 13.1%, p<0.001 (see Table 2).

The rate of death and pneumothorax were similar. Length of stay was slightly longer in the post-HFNC group (median 59 versus 54 days). There were significantly more patients with ROP in the post-HFNC group (19% vs 6.1%, p<0.001) and more patients with stage two/three ROP compared with stage one. Eleven patients in the post-HFNC group had surgery performed for ROP compared with none in the pre-HFNC group.

Following multivariate logistic regression analysis, the effect of being in the post-HFNC group remained a significant risk factor BPD development (OR 4.353, 95% CI 2.546 to 7.443, p<0.001), as did having been ventilated (OR 4.01, 95% CI 2.035-7.9, p<0.001) and being born at less than 28 weeks (OR 2.616, 95% CI 1.403-4.879). Having a birthweight <750g (OR 1.863, 95% CI 0.958-3.622, p=0.067), a 5 minute Apgar ≤5 (OR 1.801, 95% CI 0.883-3.670, p=0.105), having received ibuprofen (OR 2.05, 95% CI 0.871-4.823, p=0.1) and having early-onset sepsis (OR 3.127, 95% CI 0.683-14.312, p=0.142) did not significantly increase the chance of BPD. Adjusted odds ratios could not be calculated for ROP surgery as there were no events in the pre-HFNC group.

Table 2: Outcomes of patients analysed by cohorts pre (2010-2012) and post (2014-2016) introduction of high-flow nasal cannula.			
	2010-2012 (n=256)	2014-2016 (n=238)	Sig
Death	17/256 (6.6%)	13/236 (5.5%)	0.600 †
BPD	33/251 (13.1%)	82/232 (35.3%)	<0.001 †
Ibuprofen	18/256 (7%)	20/238 (8.4%)	0.567 †
Pneumothorax	11/256 (4.3%)	14/238 (5.9%)	0.428 †
Length of stay ✹	54 days (±38)	59 days (±49.5)	0.01 ▾
Any ROP	13/204 (6.1%)	39/205 (19%)	<0.001 †
Maximum stage of ROP			
-ROP stage 1	6/214 (2.8%)	17/205 (8.3%)	
-ROP stage 2	5/214 (2.3%)	13/205 (6.3%)	
-ROP stage 3	2/214 (0.9%)	9/205 (4.4%)	<0.001 †
Surgery for ROP	0/214 (0%)	11/205 (5.4%)	0.001 †
ROP duration of follow up ○	37+1 weeks (±4+1)	37+5 weeks (±4+1)	0.27 ✦
✹= median (interquartile range); ○=mean±SD; ✦=t-test; †=chi-squared; ▾=Mann Whitney U-test			

HFNC-eligible group analysis

From 2010 to 2016, there were 298 infants who were either had CGA<28 weeks, birthweight <750g., were ventilated or received surfactant and who did not die before discharge. 160 patients in this 'HFNC-eligible' group did not receive HFNC, and 138 in the group did receive HFNC. Regarding baseline characteristics those who received HFNC were significantly lighter (923g (±270) vs 1044g (±275) vs, p<0.001), had lesser GA (27^{+1} weeks ($\pm 2^{+0}$) vs 28^{+1} weeks ($\pm 2^{+2}$) p<0.001), and differed significantly in other characteristics as detailed in Table 3.

Table 3: Baseline characteristics of patients in 'HFNC-eligible' group; those who did not receive HFNC compared with those who received HFNC.			
	no HFNC (n=160)	HFNC (n=138)	Sig
Birthweight ○	1044g (±275)	923g (±270)	<0.001✦
Gestation ○	28^{+1} weeks ($\pm 2^{+2}$)	27^{+1} weeks ($\pm 2^{+0}$)	<0.001 ✦
Male	85/160 (53.1%)	73/138 (52.9%)	0.969 †
Multiple birth	52/160 (32.5%)	45/138 (32.6%)	0.984 †
Antenatal Steroids	140/160 (87.5%)	130/136 (95.6%)	0.014†
5 minute Apgar >5	145/160 (90.6%)	113/138 (81.9%)	0.027 †
Early onset sepsis	4/160 (2.5%)	5/138 (3.6%)	0.572 †
Received CPAP	154/160 (96.3%)	136/138 (98.6%)	0.220 †
Ventilated	142/160 (88.8%)	125/138 (90.6%)	0.606 †
Surfactant	141/160 (88.1%)	133/138 (96.4%)	0.009 †
Post-natal steroids	2/160 (1.3%)	22/138 (15.9%)	<0.001 †
○=mean±SD, ✦=t-test, †=chi-squared			

The rate of BPD was higher in those who received HFNC compared to those 'eligible' for HFNC who did not receive it (68.2% vs 21.6%, p<0.001, Table 4). Having received HFNC remained a significant risk factor for development of BPD following logistic regression analysis with an OR of 7.8 (95% CI 4.223-14.423, p<0.001). In this 'HFNC eligible' group, other significant predictors of BPD were having a birthweight <750g (OR 4.103, 95% CI 1.705-9.874, p=0.002), having a 5 minute Apgar≤5 (OR 4.252, 95% CI 1.705-9.874, p=0.003), and having received ibuprofen (OR 3.89, OR 1.460-10.364, p=0.007). The variables not associated with increased odds of BPD were gestation <26 weeks (OR 2.382, 95%

CI 0.973-5.831, p-0.057), having been intubated (OR 1.291, 95% CI 0.495-3.363, p=0.601) and early onset sepsis (4.828, 95% CI 0.679-34.334, p=0.116).

Table 4: Results from patients in 'HFNC-eligible' group; those who did not receive HFNC compared with those who received HFNC.

	no HFNC(n=160)	HFNC (n=138)	Sig
BPD	33/153 (21.6%)	90/132 (68.2%)	<0.001†
Ibuprofen	16/160 (10.0%)	23/138 (16.7%)	0.089†
Pneumothorax	11/160 (6.9%)	12/138 (8.7%)	0.557 †
Length of stay ✹	72 (±34)	92.5 (±61)	0.00 ▾
Any ROP	14/153 (9.2%)	37/134 (27.6%)	<0.0001†
Maximum stage of ROP			
-ROP stage 1	8/153 (5.2%)	14/134 (10.4%)	
-ROP stage 2	4/153 (2.6%)	12/134 (9%)	
-ROP stage 3	2/153 (1.3%)	11/134 (8.2%)	<0.001 †
Surgery for ROP	0/153 (0%)	13/134 (9.7%)	<0.001 †
ROP duration of follow up ○	38^{+1} weeks ($\pm 3^{+6}$)	39^{+4} weeks ($\pm 4^{+0}$)	0.002✦

✹= median (interquartile range); ○=mean±SD; ✦=t-test; †=chi-squared; ▾=Mann Whitney U-test

Discussion

Our study highlights that the introduction of HFNC can lead to an increase in rates of BPD among premature infants (birthweight<1500g or <30 weeks GA). This was not offset by any decrease in mortality rate. Length of stay (LOS) was also longer in the post-HFNC group. Following the introduction of HFNC, there were more infants with a 5 minute Apgar≤5 and more infants receiving CPAP, perhaps indicating higher baseline co-morbidity. However, on multivariate analysis a VLBW infant belonging to the post-HFNC group had a 4.5 fold increased risk of developing BPD, indicating that exposure to HFNC alone is a significant risk factor for development of BPD, even in the context of an increased baseline risk. However, it must also be acknowledged, that clinicians' perceptions of HFNC as 'gentler' may be contributing to slower weaning of this mode of respiratory support (compared to nCPAP), and slower subsequent transition onto low-flow 02 and room air, which would cause more BPD by our definition (i.e. oxygen dependence at 36 weeks CGA) and a longer LOS.

Our second analysis focused on those babies who were 'eligible' for HFNC (i.e. any of GA<28weeks, birthweight <750g, ventilated or received surfactant and survived to discharge) but did not receive it compared to those infants who did receive HFNC support across 2010-2016 inclusive. In this analysis, again receiving HFNC was associated with significantly more BPD. Again, in this analysis of 'HFNC-eligible' infants, LOS was longer in those who received HFNC compared to those who did not. Although baseline characteristics (smaller gestation and birthweight, higher proportion with low 5-minute Apgar, higher rates of surfactant use indicating underlying respiratory distress) showed the group receiving HFNC to be likely to develop BPD at baseline, the risk associated with receiving HFNC was again persistent after multivariate analysis, with these infants having a 7.8 fold increased risk of developing BPD. Similarly, to the analysis above, clinicians' attitude to HFNC must be kept in mind when interpreting these results.

This study also looked at the effect of HFNC on the development of ROP. Following introduction of HFNC, the rate of any ROP increased, along with the rate of more severe ROP and number of infants treated surgically. The same differences were observed when those receiving HFNC within the 'HFNC-eligible' group were compared to those who did not receive HFNC in this group. Again, while this increase in ROP can be partly attributed to a population that were generally more unwell and in receipt of more intervention (as in pre and post-HFNC analysis) or generally smaller and lesser GA (in the 'HFNC-eligible' analysis), in the context of increased BPD and likely associated increased oxygen exposure in groups receiving more HFNC, the role of HFNC in contributing to this pathology must be considered.

Limitations of our study include differences in baseline characteristics, and that we have not recorded the number of days spent on HFNC for each infant, so there may be inconsistencies in the degree of exposure. Regarding ophthalmological outcomes, this study is limited in that the individuals screening our premature infants for ROP changed during the duration of the study, however neither the indications for surgical treatment nor the single surgeon providing the surgical treatment changed throughout the entire study period for all the infants treated for ROP.

In this study, HFNC was used as a tool for weaning from CPAP. Only one available RCT evaluated a population similar to ours (birthweight≤1500g, GA<32 weeks) and employed similar weaning protocols[2]. This group showed no difference in respiratory or ophthalmological outcomes. The other two published trials[3,4] studied older infants (mean GA 31 weeks) and did not use low-flow nasal cannula Oxygen in weaning, making comparisons with this study difficult. HFNC studies also use differing flow-rates, a fact mirrored in a recent survey of centres in the UK[16], and a factor that makes comparing studies difficult. Retrospective studies have also been complicated by the fact that use of HFNC often selects out smaller, sicker infants (who have had more post-natal steroids and more ventilator courses)[5-7]. This effect was seen in our second analysis. Prospective and retrospective studies have been inconsistent in their outcomes regarding ROP[2,5-8]. In our study, use of HFNC was associated with longer LOS in both analyses. LOS was not commented on in the Soonsowad trial[2] and the two other RCTs had conflicting results[3,4]. Again it must be noted that the latter two trials examined a population dissimilar to ours.

HFNC has been shown to be ineffective as primary respiratory support for premature babies[2].Previous questions of a benefit in achieving oral feeds over CPAP have been contradicted by a recent RCT[18]. While the above studies demonstrate the lack of benefit of HFNC, we believe this study raises significant questions about its safety. In summary, this study raises the concern that use of HFNC to wean infants from CPAP may have adverse effects on respiratory and ophthalmological outcomes in premature VLBW infants. While there are many perceived benefits to HFNC, with its use becoming widespread across many neonatal units worldwide, we believe the use of HFNC as a weaning tool from CPAP needs to be further evaluated with an adequately powered RCT before it becomes the accepted norm.

Conflicts of Interest Statement:
This work has not been published or presented elsewhere. This paper had no external sources of funding and the authors have no conflicts of interest.

Corresponding Author:
Lydia Healy
Cork University Maternity Hospital,
Cork City,
Ireland
Email: healyli@tcd.ie

References:

1. Wilkinson D, Andersen C, O'Donnell CPF, De Paoli AG, Manley BJ. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev. 2016 Feb 22;2:CD006405.
2. Soonsawad S, Tongsawang N, Nuntnarumit P. Heated Humidified High-Flow Nasal Cannula for Weaning from Continuous Positive Airway Pressure in Preterm Infants: A Randomized Controlled Trial. Neonatology. 2016;110(3):204–9.
3. Abdel-Hady H, Shouman B, Aly H. Early weaning from CPAP to high flow nasal cannula in preterm infants is associated with prolonged oxygen requirement: a randomized controlled trial. Early Hum Dev. 2011 Mar;87(3):205–8.
4. Badiee Z, Eshghi A, Mohammadizadeh M. High flow nasal cannula as a method for rapid weaning from nasal continuous positive airway pressure. Int J Prev Med. 2015;6:33.
5. Sasi A, Malhotra A. High flow nasal cannula for continuous positive airway pressure weaning in preterm neonates: A single-centre experience. J Paediatr Child Health. 2015 Feb;51(2):199–203.

6. Taha DK, Kornhauser M, Greenspan JS, Dysart KC, Aghai ZH. High Flow Nasal Cannula Use Is Associated with Increased Morbidity and Length of Hospitalization in Extremely Low Birth Weight Infants. J Pediatr. 2016 Jun;173:50-55.e1.
7. Heath Jeffery RC, Broom M, Shadbolt B, Todd DA. Increased use of heated humidified high flow nasal cannula is associated with longer oxygen requirements. J Paediatr Child Health. 2017 Dec;53(12):1215–9.
8. Hoffman SB, Terrell N, Driscoll CH, Davis NL. Impact of High-Flow Nasal Cannula Use on Neonatal Respiratory Support Patterns and Length of Stay. Respir Care. 2016 Oct;61(10):1299–304.
9. Verder H, Robertson B, Greisen G, Ebbesen F, Albertsen P, Lundstrom K, et al. Surfactant Therapy and Nasal Continuous Positive Airway Pressure for Newborns with Respiratory Distress Syndrome. N Engl J Med. 1994 Oct 20;331(16):1051–5.
10. Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB. Low-Dose Dexamethasone Facilitates Extubation Among Chronically Ventilator-Dependent Infants: A Multicenter, International, Randomized, Controlled Trial. Pediatrics. 2006 Jan 1;117(1):75–83.
11. Wilkinson AR, Haines L, Head K, Fielder AR. UK retinopathy of prematurity guideline. Eye. 2009 Nov;23(11):2137–9.
12. IBM SPSS Statistics Version 25. Armonk, NY: IBM Corp; 2017.
13. Marshall DD, Kotelchuck M, Young TE, Bose CL, Kruyer L, O'Shea TM. Risk factors for chronic lung disease in the surfactant era: a North Carolina population-based study of very low birth weight infants. North Carolina Neonatologists Association. Pediatrics. 1999 Dec;104(6):1345–50.
14. Rojas MA, Gonzalez A, Bancalari E, Claure N, Poole C, Silva-Neto G. Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease. J Pediatr. 1995 Apr;126(4):605–10.
15. Oh W, Poindexter BB, Perritt R, Lemons JA, Bauer CR, Ehrenkranz RA, et al. Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremely low birth weight infants. J Pediatr. 2005 Dec;147(6):786–90.
16. Shetty S, Sundaresan A, Hunt K, Desai P, Greenough A. Changes in the use of humidified high flow nasal cannula oxygen. Arch Dis Child Fetal Neonatal Ed. 2016 Jul;101(4):F371-372.
17. Roberts CT, Owen LS, Manley BJ, Frøisland DH, Donath SM, Dalziel KM, et al. Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants. N Engl J Med. 2016 Sep 22;375(12):1142–51.
18. Glackin SJ, O'Sullivan A, George S, Semberova J, Miletin J. High flow nasal cannula versus NCPAP, duration to full oral feeds in preterm infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2017 Jul;102(4):F329–32.