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Nasal High-Flow Therapy as Primary Respiratory Support for Preterm Infants without the Need for Rescue with Nasal Continuous Positive Airway Pressure

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Keywords
Preterm infant · Bronchopulmonary dysplasia · Continuous positive airway pressure · Nasal high-flow therapy · Mechanical ventilation

Abstract
Aim: To evaluate the effectiveness of nasal high-flow therapy (nHFT) as primary respiratory support for preterm infants with respiratory distress syndrome (RDS) in two tertiary neonatal units. ***Methods:*** A retrospective outcome analysis of initial respiratory support strategies was performed in two tertiary neonatal units in the UK: John Radcliffe Hospital (JRH), Oxford and St Peter's Hospital (SPH), Chertsey. Infants born between 28^{+0} and 36^{+6} weeks gestational age (GA) between May 2013 and June 2015 were included. ***Results:*** A total of 381 infants, 191 from JRH and 190 from SPH, were analysed. Infants were stabilised in the delivery room using mask continuous positive airway pressure followed by nHFT. Endotracheal intubation was performed according to local protocols, depending on the severity of RDS. There were significant differences in initial intubation rates according to GA (26% JRH vs. 16.9% SPH, $p < 0.001$ for babies <32 weeks GA, and 8.2% JRH vs. 6.5% SPH, $p < 0.001$ for babies >32 weeks GA); however, most infants were successfully transitioned to nHFT. Intubation rates during the first 72 h were comparable between centres (14.7% JRH vs. 11.1% SPH, $p = 0.29$). There were no differences in neonatal morbidities, including air leak, duration of oxygen supplementation, bronchopulmonary dysplasia, sepsis, retinopathy of prematurity, intraventricular haemorrhage, necrotising enterocolitis, or median time to full-suck feeds. ***Conclusion:*** Use of nHFT for primary respiratory support, without use of nasal continuous positive airway pressure as "rescue" treatment, resulted in intubation rates lower or comparable to published data from randomised controlled trials.

Introduction

Bronchopulmonary dysplasia (BPD), a main respiratory complication of prematurity, is associated with mechanical ventilation (MV) [1]. Infants with BPD suffer significant respiratory morbidity and neurocognitive impairment into childhood [2, 3]. Non-invasive ventilation

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(NIV) and the use of positive end-expiratory pressure is known to reduce cell damage and lung inflammation, stimulates surfactant metabolism, and hence is considered an important part of a lung-protective ventilation strategy from birth [4, 5]. Positive end-expiratory pressure can be applied as nasal continuous positive airway pressure (nCPAP), nasal high-flow therapy (nHFT), or non-invasive positive pressure ventilation [6].

Evidence from clinical trials has shown that there are significant benefits of initial NIV with nCPAP over intubation and MV, showing a reduction in duration of ventilatory support and trends towards improved survival without BPD [7]. nCPAP has become the gold standard for NIV of preterm infants over the last 10 years. Randomised controlled trials (RCTs) comparing MV to nCPAP for treatment of respiratory distress syndrome (RDS) at birth in very preterm infants have shown that in more than half of these infants, intubation and MV can be avoided by using nCPAP [8, 9].

Unfortunately, nCPAP delivery systems are associated with significant risk of nasal trauma [10, 11]. Imbulana et al. [11] assessed the incidence of and risk factors for nasal injury in preterm infants. In their systematic review including 45 trials, the reported incidence of nasal injury in preterm infants receiving nCPAP ranged from 20 to 100%. The main risk factors for nasal erosions were lower gestational age (GA) (<30 weeks) or birth weight <1,500 g. Pooled analysis of 7 RCTs found that nHFT was associated with significantly reduced rates of nasal injury when compared to nCPAP (RR 0.46, 95% CI 0.37–0.58; NNT 7, 95% CI 6–10).

The proposed mechanisms of action of nHFT are effective nasopharyngeal CO_2 washout, reduction in inspiratory resistance in the upper airways, and a reduction in the work of breathing, comparable to the nCPAP effect [12–14]. nHFT seems to be better tolerated [15, 16]. Consequently, the use of nHFT has expanded significantly: around 77% of surveyed units in the UK reported the use of nHFT in 2013 [17]. Additionally, the feasibility of stabilisation of preterm babies on nHFT in the delivery room has been demonstrated [18].

Wilkinson et al. [19] summarised the evidence around neonatal nHFT use in a recently updated Cochrane Review. There were similar failure rates post extubation with nHFT and with nCPAP, with a trend towards less adverse pulmonary and non-pulmonary outcomes in the nHFT groups. Additionally, there was a reduction in the incidence of pneumothoraces with nHFT (typical RR 0.35, 95% CI 0.11–1.06), whilst duration of oxygen supplementation and hospital stay were comparable [19]. However, the evidence for infants born <27 weeks GA is still very limited [20, 21].

Recently, results from a multinational, multicentre RCT by Roberts et al. [22] investigating the use of nHFT as primary respiratory support following initial stabilisation suggested that nHFT appears to be inferior to nCPAP in preventing primary intubation in preterm infants. According to the trial's protocol, deteriorating babies on nHFT required to be "rescued" with nCPAP to prevent intubation, suggesting that nCPAP was the more effective form of NIV. By contrast, a similar study by Lavizzari et al. [23] found that in a similar group of infants, nHFT was as effective as nCPAP or bilevel nCPAP in keeping preterm babies from being mechanically ventilated.

Therefore, our group of authors, working in centres where nHFT has been well established for over 12 years, sought to study our experience in supporting preterm infants with nHFT in comparison to the published literature.

Patients and Methods

To evaluate the effectiveness of nHFT as primary respiratory support for preterm infants with RDS, a retrospective observational study was performed in two tertiary neonatal units in the UK: John Radcliffe Hospital (JRH), Oxford and St Peter's Hospital (SPH), Chertsey. Infants born between May 2013 and June 2015 were included if they met the following inclusion criteria: inborn, GA 28^{+0} to 36^{+6} weeks, <24 h old at the start of nHFT, and not having received previous endotracheal ventilation. Infants were excluded if they had major congenital anomalies, if they were intubated at birth, and if they had previously received other forms of NIV support.

Clinicians in both centres have found nCPAP to be poorly tolerated by infants >28 weeks GA compared to nHFT. For the purpose of consistency of our clinical management, we have persisted with the use of nHFT for more than a decade in both centres. Details of the use of nHFT in relation to nCPAP have recently been published [16]. Both centres, however, occasionally use nCPAP in infants <28 weeks (at their clinician's discretion), and therefore this GA group was not included.

Data were gathered from medical notes and the BadgerNet platform (Clevermed, Edinburgh, UK). Maternal and neonatal demographics were recorded. All data sets were anonymised. Ethical approval was not necessary as this was an evaluation of current practice.

According to local policy, infants breathing spontaneously at birth were managed with either mask CPAP or non-invasive positive pressure ventilation, delivered through a T-piece device (Neopuff; Fisher & Paykel, Auckland, New Zealand). Both centres use nHFT (Vapotherm Precision Flow, Exeter, NH, USA) as primary respiratory support after birth.

Resuscitation practices at birth in both centres complied with the European Resuscitation Council guidelines [24]. An initial fraction of inspired oxygen (FiO_2) of 0.21 was used and increased

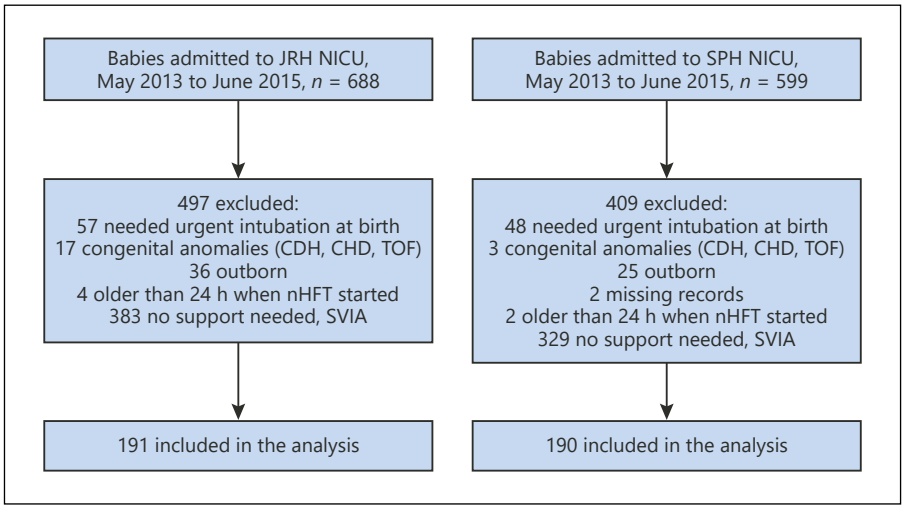

Fig. 1. Consort diagrams for John Radcliffe Hospital (JRH) and St Peter's Hospital (SPH). CDH, congenital diaphragmatic hernia; CHD, congenital heart defect; NICU, neonatal intensive care unit; SVIA, self-ventilating in air; TOF, tetralogy of Fallot.

according to recommended saturation limits for time of life, with initial inflation pressures of 20 cm H_2O (up to 30 cm H_2O) and a positive end-expiratory pressure of 5 cm H_2O.

Following admission to the special care baby unit, neonates were started on nHFT with an initial flow rate of 6–7 L/min and FiO_2 for targeting peripheral oxygen saturation (SpO_2) 88–93% (SpO_2 limits). Both flow rate and FiO_2 were then adjusted according to blood gas analysis and clinical condition.

Targeted surfactant (200 mg/kg of Porfactant alpha; Chiesi Farmaceutici, Parma Italy) was considered for neonates showing clinical signs of RDS (either FiO_2 requirement >0.4 or >0.3 to reach SpO_2 targets and/or significant chest X-ray changes). Less invasive surfactant administration (LISA) was only available at SPH. At JRH, the INSURE method was practised for surfactant delivery. However, this method was often followed by a period of MV and therefore routinely recorded as intubation. Intravenous caffeine citrate (20 mg/kg loading dose and maintenance dose of 10 mg/kg/day) was routinely commenced for prevention and treatment of apnoea of prematurity in all neonates <32 weeks within 4 h of birth at SPH and JRH (target time) and discontinued at 34 weeks corrected GA in the absence of ongoing apnoea at both centres.

The primary outcome was intubation rate within 72 h of starting nHFT. The recorded reasons for intubation were increased FiO_2 (>0.4), pH ≤7.2 and/or partial pressure of CO_2 >60 mm Hg, recurring episodes of apnoea, urgent need for intubation and MV, or clinician's decision.

The prespecified secondary outcomes were need for MV at any time, intubation within 72 h in predefined GA subgroups (below and above 32 weeks GA), total days of respiratory support, last day of supplemental oxygen received (recorded as day of life and postmenstrual age at final cessation of oxygen supplementation), discharge home with oxygen, treatment with postnatal intravenous corticosteroids, age at reaching full-suck feeding (defined as the day of life on which no intravenous fluids or nasogastric/orogastric feeds are given), whether nasogastrically fed at discharge home, and weight at discharge.

Data regarding significant neonatal morbidities included BPD (supplemental oxygen requirement and/or receiving respiratory support at 28 days of life and 36 weeks postmenstrual age), air leak (pneumothorax/pneumomediastinum/pulmonary interstitial emphysema), sepsis (defined as positive blood culture and treatment with intravenous antibiotics for at least 48 h, meningitis, patent ductus arteriosus treated with medication and/or surgery, necrotising enterocolitis Bell's stage ≥2, intraventricular haemorrhage (grade III–IV), cystic periventricular leukomalacia or posthaemorrhagic ventricular dilatation, retinopathy of prematurity requiring laser treatment, and death.

Statistical Analysis

The sample size was predetermined by the time frame and birth rate over the 2 years, which corresponded to the time frame of the recruitment of the larger of the two RCTs (from May 2013 to June 2015) [15]. The data of infants from the two centres, JRH and SPH, were compared as two independent groups. We primarily aimed to assess whether the intubation rates and adverse outcomes were comparable between both centres.

All variables were tested for normal distribution with the Kolmogorov-Smirnov test. Comparisons of the means were performed with Student's *t* test for normally distributed variables and the Mann-Whitney U test for non-Gaussian variables. The χ^2 test was used for categorical variables. The analysis was performed using SPSS 22 version (SPSS GmbH Software; IBM, Armonk, NY, USA).

Results

Between May 2013 and June 2015, there were 688 infants admitted to the neonatal intensive care unit of JRH; 497 were excluded from the analysis (57 needed urgent intubation at birth, 17 were born with congenital anomalies, 36 were outborn, 4 were older than 24 h when nHFT was started, and 383 needed no respiratory support or oxygen supplementation during the hospital stay). At

Table 1. Infant and maternal characteristics of the two centres

Infant characteristics	JRH (n = 191)	SPH (n = 190)	p value
Mean GA, weeks	32.9±2.2	32.3±2.4	0.01
GA, weeks	33 (31–34.6)	32.4 (30.3–34.3)	<0.001
GA <32 weeks	69/191 (36.1%)	83/190 (43.7%)	0.13
Mean birth weight, g	2,018.6±663	1,770.4±576	<0.001
Male sex	113/191 (59.2%)	111/190 (58.4%)	0.88
Multiple births	70/191 (36.6%)	80/190 (42.1%)	0.28
Median 1-min Apgar score	8 (6–9)	8 (6–9)	0.167
Median 5-min Apgar score	10 (9–10)	9 (8–10)	<0.001
Mean starting cord pH	7.29±0.1	7.21±0.13	<0.001
Median FiO_2 prior to nHFT	0.25 (0.21–0.35)	0.3 (0.21–0.35)	0.16
Caffeine in first 24 h	95/191 (49.7%)	71/190 (37.4%)	0.02
Primigravida	68/191 (35.6%)	79/190 (41.6%)	0.007
Antenatal steroids	125/191 (65.4%)	133/190 (70%)	0.34
Caesarean section	128/191 (67.0%)	122/190 (64%)	0.36
PROM >24 h	26/191 (13.6%)	25/190 (13.2%)	0.89

Data for JRH and SPH are presented as mean ± standard deviation, median (interquartile range), or n (%). FiO_2, fraction of inspired oxygen; GA, gestational age; JRH, John Radcliffe Hospital; nHFT, nasal high-flow therapy; PROM, premature rupture of membranes; SPH, St Peter's Hospital.

Table 2. Main outcomes (intubation within 72 h) of the two centres

Intubation within 72 h	JRH (n = 191)	SPH (n = 190)	Both centres combined	p value
All infants	28/191 (14.7%)	21/190 (11.1%)	49/381 (12.8%)	0.29
GA <32 weeks	18/69 (26%)	14/83 (16.9%)	32/152 (21%)	<0.001
GA >32 weeks	10/122 (8.2%)	7/107 (6.5%)	17/229 (7.4%)	<0.001

Data are presented as n (%). GA, gestational age; JRH, John Radcliffe Hospital; SPH, St Peter's Hospital.

Table 3. Reasons for intubation of two centres (only limited data available)

Reasons for intubation	JRH (n = 191)	SPH (n = 190)	p value
Apnoea	1/191 (0.5%)	4/190 (2.1%)	0.18
FiO_2 >0.4	16/191 (8.4%)	18/190 (9.5%)	0.56
Respiratory acidosis	7/191 (3.7%)	3/190 (1.6%)	0.2
Urgent need for intubation	3/191 (1.6%)	0	0.08
Clinician's decision to intubate	8/191 (4.2%)	9/190 (4.7%)	0.79

Data are presented as n (%). FiO_2, fraction of inspired oxygen; JRH, John Radcliffe Hospital; SPH, St Peter's Hospital.

SPH, 599 infants were admitted during the study period; 409 were excluded from the analysis (48 needed urgent intubation at birth, 3 had congenital anomalies, 25 were outborn, 2 had missing records, 2 were older than 24 h when nHFT was started, and 329 needed no respiratory support during the hospital stay). A total of 381 infants, 191 from JRH and 190 from SPH, were analysed (Fig. 1).

There were no differences between infants from either JRH or SPH regarding the use of antenatal steroids, caesarean section, premature rupture of membranes, male

Table 4. Respiratory and feeding outcomes of the two centres

Other outcomes	JRH (n = 191)	SPH (n = 190)	p value
Median time of respiratory support, days	3 (2–6)	5 (2–9)	<0.001
Median age at cessation of oxygen, days	2 (0–4)	2 (1–7)	0.87
Discharged home with oxygen	1/191 (0.5%)	6/190 (3.2%)	0.06
Median age at full-suck feeding, days	22 (12–36)	24 (13–41)	0.52
Discharged home with gastric tube feeding	34/191 (17.8%)	2/190 (1.1%)	<0.001
Weight at discharge, g	2,373.6±430	2,219.1±389	<0.001

Data are presented as mean ± standard deviation, median (interquartile range), or n (%). JRH, John Radcliffe Hospital; SPH, St Peter's Hospital.

Table 5. Neonatal adverse events and outcomes of the two centres

Adverse events	JRH (n = 191)	SPH (n = 190)	p value
Death before discharge	0	1/190 (0.5%)	0.32
FiO_2, respiratory support, or both at 36 weeks	5/191 (2.6%)	12/190 (6.3%)	0.16
Air leak	8/191 (5.8%)	5/190 (2.6%)	0.4
Postnatal steroids	0	1/190 (0.5%)	0.32
Nasal trauma	0	0	
PDA requiring treatment	2/191 (1%)	1/190 (0.5%)	0.57
Confirmed sepsis	15/191 (7.9%)	14/190 (7.4%)	0.9
Necrotising enterocolitis	4/191 (2.1%)	1/190 (0.5%)	0.25
Intestinal perforation	0	0	
Retinopathy of prematurity grade >2	0	0	
Intraventricular haemorrhage 3–4	1/191 (0.5%)	2/190 (1.1%)	0.22
Periventricular leukomalacia	1	0	0.32

Data are presented as n (%). FiO_2, fraction of inspired oxygen; JRH, John Radcliffe Hospital; PDA, patent ductus arteriosus; SPH, St Peter's Hospital.

sex, and multiple births (Table 1). Mean birth weight and mean GA differed between JRH and SPH (2,019 vs. 1,770 g, $p < 0.001$, and 32.9 vs. 32.3 weeks, $p = 0.01$, respectively), but not the proportion of babies born <32 weeks GA (36.1 vs. 43.7%, $p = 0.13$) (Table 1).

Intubation rates were comparable between the two centres across all GA groups (14.7% JRH vs. 11.1% SPH, $p = 0.29$) (Table 2). There were significant differences according to GA (26% JRH vs. 16.9% SPH, $p < 0.001$ for babies <32 weeks GA, and 8.2% JRH vs. 6.5% SPH, $p < 0.001$ for babies >32 weeks GA) (Table 2). Eleven babies at SPH and none at JRH were given surfactant via LISA. The reasons for intubation and ventilation were clearly documented in only a small proportion of infants (Table 3).

There were no differences in mortality, BPD, duration of oxygen supplementation, proportion of babies discharged on home oxygen, or median age at full-suck feeding between centres (Table 4). There were no differences in adverse outcomes (air leak, patent ductus arteriosus, sepsis, retinopathy of prematurity, intraventricular haemorrhage, and necrotising enterocolitis) (Table 5).

Discussion

Our retrospective study demonstrates that the use of nHFT for primary respiratory support in infants born >28 weeks of GA, without use of nCPAP as "rescue" treatment, resulted in intubation rates lower than or comparable to published data. There were no significant differences regarding pulmonary or extrapulmonary outcomes between our centres and the two aforementioned RCTs [22, 23]. The intubation rate was lower at SPH, even

though the infants in that centre had lower birth weights, were more premature, and received caffeine in smaller proportion within the first 24 h compared to JRH.

Our findings are consistent with those of Lavizzari et al. [23] who randomised 316 premature infants (29^{+0} to 36^{+6} weeks GA) to receive either nHFT of 4–6 L/min or nCPAP/bilevel nCPAP of 4–6 cm H_2O. There were no significant differences in intubation rates or other secondary outcomes. The authors concluded that nHFT appears to have similar efficacy and safety as nCPAP when used as primary treatment of mild to moderate RDS.

Conversely, our findings differ from those reported by Roberts et al. [22], who found nHFT to be inferior to nCPAP because more infants in the nHFT group (71 of 278 infants [25.5%]) had reached the prespecified treatment failure criteria compared to the nCPAP group (38 of 286 infants [13.3%]) and therefore, as per protocol, were given "rescue" by nCPAP to prevent intubation ($p < 0.001$) [18]. The rate of intubation within 72 h did not differ significantly between the nHFT and the nCPAP group (15.5 and 11.5%, respectively, $p = 0.17$), but the study suggests that infants supported by nHFT would have been intubated unless supported by nCPAP. In our study, the intubation rates were comparable to those by Roberts et al. [22] (JRH 14.7% vs. SPH 11.1%, $p = 0.29$), without the use of nCPAP as rescue.

We believe it of importance to point out that Roberts et al.'s study included centres with little or no experience with nHFT. The difference in familiarity with the system, together with the permissive failure criteria for nHFT in their trial, may have contributed to nHFT being labelled as inferior to nCPAP as a primary mode of respiratory support.

At SPH, the LISA procedure may have further reduced the rate of intubation in babies on nHFT. A reduction in intubation rates with the use of LISA has been previously observed in babies <32 weeks of GA [25]. Recent meta-analyses comparing LISA with the standard method of surfactant delivery found that infants treated with LISA have less need for MV, death, or BPD at 36 weeks among survivors [25, 26].

Worryingly, NIV in the form of nCPAP might not be the answer to long-term lung injury. In a large cohort following preterm infants born between 1992 and 2005 with the mean GA of 25 weeks, Doyle et al. [27, 28] showed that despite substantial increases in the use of less invasive ventilation after birth, there was no significant decline in oxygen dependence at 36 weeks and no significant improvement in lung function in childhood at 8 years of age. However, nHFT has increasingly been used in their region since then, and the association of such a change with long-term lung function remains to be determined. Today's respiratory care package for preterm infants, compared to 2005 and before, consists of very different elements. In particular, the many benefits of nHFT have only recently been recognised, and an association of nHFT with long-term lung function remains to be determined.

Our study has several limitations. Due to the retrospective data collection we were not able to explore the indications for intubation in the subgroup of intubated infants. We were not able to compare the use of nHFT with other NIV modes either. As the study describes outcomes in two centres that have been using nHFT without the use of nCPAP in this GA group for more than a decade, it is not possible to exclude bias of the nursing and medical staff towards this mode of NIV. The exclusive use of nHFT makes a centre well versed in its use, and therefore it might not be possible to replicate these outcomes in a different centre with, for instance, a long-standing history of nCPAP use.

In conclusion, our two-centre observational study illustrates that preterm infants >28 weeks GA, when treated in centres well accustomed to the use of nHFT, can be successfully supported by nHFT, without the use of nCPAP as a "rescue" treatment.

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