

High-Flow Nasal Cannulae for Respiratory Support of Preterm Infants: A Review of the Evidence

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Key Words

Infant, premature · Continuous positive airway pressure · High-flow nasal cannulae · Intensive care, neonatal

Abstract

Background: High-flow nasal cannulae (HFNC) are gaining in popularity as a form of non-invasive respiratory support for preterm infants in neonatal intensive care units around the world. They are proposed as an alternative to nasal continuous positive airway pressure (NCPAP) in a variety of clinical situations, including post-extubation support, primary therapy from birth and 'weaning' from NCPAP. **Objectives:** To present and discuss the available evidence for the use of HFNC in the preterm population. **Methods:** An internet-based literature search for relevant, original research articles (both randomised studies and not) on the use of HFNC in preterm infants was undertaken. **Results:** A total of 19 studies were included in the review. Distending pressure generated by HFNC in preterm infants increases with increasing flow rate and decreasing infant size and varies according to the amount of leak around the prongs. HFNC may be as effective as NCPAP at improving respiratory parameters such

as tidal volume and work of breathing in preterm infants, but probably only at flow rates >2 litres/min. The efficacy and safety of HFNC in preterm infants remain to be determined. **Conclusions:** There is growing evidence of the feasibility of HFNC as an alternative to other forms of non-invasive ventilation in preterm infants. However, there remains uncertainty about the efficacy and safety of HFNC in this population. Until the results of larger randomised trials are known, widespread use of HFNC to treat preterm infants cannot be recommended.

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Introduction

Binasal cannulae that deliver high gas flows (high-flow nasal cannulae, HFNC) are becoming a popular form of respiratory support for preterm infants. Definitions of 'high' flow vary; a flow rate >1 litre/min was used in the recent Cochrane review [1]. HFNC are used to treat older children, particularly those with viral respiratory tract infections, and there is increasing evidence of their efficacy in this population [2–4]. The clinical application

of HFNC has been described for neonatal intensive care units in the USA [5–7], United Kingdom [8] and Australia and New Zealand [9]. In preterm infants, HFNC are used as a primary support for respiratory distress syndrome (RDS), for treating apnoea of prematurity (AOP), to support preterm infants after extubation and to wean from nasal continuous positive airway pressure (NCPAP). HFNC are also embraced by smaller, non-tertiary nurseries because they are easier to apply than NCPAP [10] and because they allow greater access to the baby's face, which may improve feeding and bonding. The commercially available HFNC systems are open systems with leaks at the nose and mouth. These systems effectively humidify delivered gas [11, 12] and provide a means to blend oxygen with air. A range of nasal prong sizes is available.

The Cochrane review of HFNC use in preterm infants [1] included only four small randomised studies comparing HFNC with other forms of respiratory support in a total of 177 preterm infants; three of these studies are published [13–15] and one is unpublished [Nair and Karna, unpubl. data]. Heterogeneity of interventions and outcomes made meta-analysis inappropriate. The authors concluded that there is insufficient evidence to establish the safety or effectiveness of HFNC as a form of respiratory support in preterm infants.

We aim to provide a comprehensive review of the available evidence for the use of HFNC in preterm infants, including and beyond data derived from randomised trials.

Search Strategy

An internet-based literature search for relevant, original research articles on the use of HFNC in preterm infants was performed (last completed 29 March 2012). We searched PubMed, Medline, CINAHL, Embase and the Cochrane Library using the search terms [high flow OR high-flow] AND nasal cannula*, with no language restriction. This search produced a total of 138 individual articles. We excluded studies not relevant to the preterm population, letters to the editor, review articles or commentaries and articles only available as abstracts. Of the remaining 15 studies, 12 were clinical trials, 1 was an animal study (Frizzola et al. [16]) and 2 were bench-top studies (Hasan and Habib [17] and Volsko et al. [18]). In addition, we included data from the unpublished clinical trial by Nair and Karna that was presented in the Cochrane review. A further three clinical studies (Locke et

al. [19], Boumecid et al. [20] and Wilkinson et al. [21]) were found by examining the reference lists of the retrieved articles. Thus, a total of 19 studies are included in this review; 16 of these are clinical studies that are detailed in the Appendix and have been assigned a level of evidence [22].

How Much Distending Pressure Is Generated by HFNC in Preterm Infants?

Some clinicians are concerned by the generation of unpredictable pulmonary distending pressures when HFNC is applied to newborn infants. Finer [23] and Finer and Mannino [24] noted that with ventilator-generated or bubble NCPAP, the delivered pressure will not exceed the set pressure, but there is no such reassurance with HFNC. Data on HFNC pressure generation come from small, observational, crossover, animal and in vitro studies, which have mainly used oesophageal pressure monitoring to estimate intrapulmonary pressures.

Locke et al. [19] raised concerns about pulmonary over-distension when they measured a mean oesophageal pressure of 9.8 cm H₂O using flow rates of 2 litres/min in 13 preterm infants. According to more recent studies, pressures generated by HFNC were similar to or less than those commonly set with NCPAP [18, 21, 25, 26]. HFNC pressures increase with increasing flow rates [16–18, 25–27] and also with decreasing infant weight [21]. Sreenan et al. [28] studied 40 preterm infants on HFNC and determined the flow rate required to generate an end-expiratory oesophageal pressure equal to that measured during NCPAP at 6 cm H₂O. Wilkinson et al. [21] measured pharyngeal pressures in 18 premature infants receiving HFNC at 2–8 litres/min with the Fisher & Paykel system (Fisher & Paykel Healthcare, Auckland, New Zealand), however without the pressure-limiting valve attached that has lately been included with this circuit, and also produced a formula to predict pressure. However, Sreenan et al. [28] predict that 1.6 litres/min in a 1-kg infant will produce a distending pressure comparable to NCPAP at 6 cm H₂O, whereas Wilkinson et al. [21] predict that 2 litres/min will produce a pressure of only 2.8 cm H₂O in a baby of the same size.

These contrasting results may be due to a number of factors; the published studies have small sample sizes, use different modes and sites of pressure measurement (oral, pharyngeal, tracheal or oesophageal), study infants with heterogeneous gestational ages and weights and study a variety of flow rates and nasal prong sizes. Hence, results

from these studies should be interpreted with caution. It must be recognized that pressures will vary considerably depending on leak at the mouth (i.e. mouth open vs. closed) [16, 17, 21, 26, 29] and presumably also in the presence of nasal obstruction and that these changes in delivered pressure cannot be continuously controlled for by clinicians.

HFNC and Respiratory Mechanics

Although flow rates of only 0.5–2 litres/min were studied, Locke et al. [19] were able to demonstrate both the generation of distending pressure with HFNC and a reduction in thoraco-abdominal asynchrony with larger prongs and increased flow. Woodhead et al. [15] performed a small randomized crossover trial of the heated and humidified Vapotherm system (Vapotherm Inc., Stevensville, Md., USA) versus ‘standard’ unhumidified HFNC; infants in the Vapotherm group had lower respiratory effort scores, which were based on the respiratory rate and chest retractions of the infant, demonstrating the need for proper heating and humidification of delivered gases.

Boumeqid et al. [20] studied 19 preterm infants, comparing variable-flow NCPAP at 5 cm H₂O to conventional NCPAP at 5 cm H₂O and HFNC at 2 litres/min, applied in a random order. Outcomes included tidal volume (V_t), thoraco-abdominal synchrony, respiratory rate and inspiratory times (obtained from respiratory inductive plethysmography). The variable-flow NCPAP increased V_t and improved thoraco-abdominal synchrony compared to the other modalities, but there was no difference between conventional NCPAP and HFNC.

Saslow et al. [30] compared the V_t in premature neonates supported with either HFNC or NCPAP. Eighteen preterm neonates with a birth weight <2 kg received either Vapotherm or NCPAP (Infant Bird ventilator, VIASYS Healthcare Inc., Conshohocken, Pa., USA) in a random order and then crossed over to the other treatment. V_t was measured using respiratory inductive plethysmography at HFNC flow rates of 3–5 litres/min and NCPAP at 6 cm H₂O. No differences were found between the two treatments at any setting, leading the authors to conclude that HFNC provided comparable respiratory support to NCPAP in this population.

Lampland et al. [27] compared NCPAP at 6 cm H₂O with HFNC at 1–6 litres/min in a group of 15 preterm infants with RDS. Measured parameters included heart rate, respiratory rate, fraction of inspired oxygen, arterial

oxygen saturation and an ‘RDS score’. The only significant finding was the development of tachypnoea with HFNC at flow rates of 1–2 litres/min ($p < 0.02$). Three patients also developed apnoea and increased oxygen needs when weaned to 1 litre/min.

Frizzola et al. [16] studied gas exchange with HFNC therapy in an animal study. Thirteen neonatal piglets (weight 2–6 kg) with induced lung injury were treated with HFNC at 2–8 litres/min in both high- and low-leak settings. The impact of increasing flow on CO₂ removal and oxygenation was independent of the tracheal pressures generated. Both ventilation and oxygenation improved in a flow-dependent manner, independent of leak, and oxygenation was particularly improved in the presence of higher leak. This is interesting, as it indicates improved efficacy with higher leak (and less pressure).

In summary, humidified HFNC systems may have comparable effectiveness to conventional NCPAP in improving important clinical parameters in preterm infants, but probably only at flow rates above 2 litres/min. Dead-space washout from HFNC may be an important additional mechanism of action to distending pressure generation, although this has not been extensively studied.

Clinical Uses of HFNC in Preterm Infants

HFNC to Prevent Extubation Failure

HFNC has been proposed as an alternative to NCPAP in neonatal intensive care units for preventing extubation failure. This is despite there being little published evidence to support the effectiveness of HFNC, while a large body of evidence has demonstrated the efficacy of NCPAP in this role [31]. Campbell et al. [13] performed the only randomised controlled trial (RCT), comparing HFNC (which was non-heated, but humidified) to Infant Flow NCPAP (VIASYS Healthcare) as post-extubation support in 40 infants with birth weight <1,250 g. Significantly more infants in the HFNC group required re-intubation within 7 days than in the NCPAP group (12/20 vs. 3/20, $p = 0.003$). Infants receiving HFNC required higher oxygen concentrations and experienced more episodes of apnoea and bradycardia. Flow rates were calculated from the formula of Sreenan et al. [28] and ranged from 1.4 to 1.7 litres/min. These flow rates are much lower than those in current clinical use [9, 10] and may explain the poor performance of HFNC in this study.

Miller and Dowd [14] compared the ability of Vapotherm and Fisher & Paykel HFNC to prevent re-intubation in premature infants in a prospective RCT funded by the two manufacturers. They found a failure rate of 18% in the Fisher & Paykel group and 9% in the Vapotherm group, but the study was a pilot and not powered to find statistical differences. In the randomized trial of Woodhead et al. [15], no preterm infants receiving Vapotherm failed, but 7 failed standard HFNC. The retrospective, observational study of Holleman-Duray et al. [7] comparing HFNC to NCPAP found no difference in rates of extubation failure, and a retrospective review by Shoemaker et al. [6] found that more infants were intubated for failing NCPAP compared to HFNC (40 vs. 18%; $p = 0.03$) following the introduction of HFNC. Larger, prospective RCTs of HFNC as post-extubation support are currently under way.

HFNC as Primary Therapy for RDS or AOP

A few small, non-randomised studies have included infants being treated with HFNC for early or stable RDS or for AOP. The only RCT data are from the unpublished study by Nair and Karna, which was included in the recent Cochrane review. There are no published RCTs that examine the use of early HFNC compared to NCPAP or supplemental oxygen alone.

Saslow et al. [30] conducted a crossover study of preterm neonates who were medically stable on HFNC or NCPAP for treatment of mild RDS, bronchopulmonary dysplasia (BPD) or AOP and showed no difference in V_t on either device. The study of Lampland et al. [27] compared NCPAP at 6 cm H_2O to HFNC at 1–6 litres/min in a group of 15 preterm infants with stable RDS and showed only the development of tachypnoea at HFNC ≤ 2 litres/min. Sreenan et al. [28] also compared HFNC to NCPAP for AOP and showed no difference in apnoea severity. The retrospective review of Shoemaker et al. [6] found that ventilator days per patient were decreased (mean 19.4 vs. 9.9 days; $p = 0.03$) following the introduction of HFNC as early respiratory support.

In Nair and Karna's RCT [unpubl. data], 67 preterm infants who required NCPAP in the first 6 h of life for RDS were randomised to continue NCPAP at 5–6 cm H_2O ($n = 34$) or receive Vapotherm at 5–6 litres/min ($n = 33$). The trial ceased early due to the recall of Vapotherm circuits by the manufacturer (see below). Four infants in each group (approx. 12%) met pre-determined failure criteria and were intubated. Secondary outcomes, including duration of hospitalisation and the combined outcome of death or BPD, did not differ between the groups.

In summary, the use of HFNC as a primary therapy from birth requires further research. If HFNC is shown to be safe and efficacious, it may be a potentially easy-to-use alternative to NCPAP. Future trials should compare HFNC to NCPAP in this role, as well as to treatment with supplemental oxygen alone.

HFNC to Wean from NCPAP

Weaning or 'stepping down' from NCPAP to HFNC treatment is common. Presumably this practice stems from the belief that HFNC is a mild form of NCPAP, and also that convalescing preterm infants with evolving BPD will benefit from the smaller nasal prongs and less bulky device. We found only two single-centre studies of this use of HFNC.

Abdel-Hady et al. [32] randomised 60 preterm infants (≥ 28 weeks' gestation) who were stable on NCPAP at 5 cm H_2O with fraction of inspired oxygen < 0.30 for at least 24 h into two groups. The NCPAP group was kept on NCPAP until they required no supplemental oxygen for 24 h and then placed in air. The HFNC group was changed to humidified HFNC at 2 litres/min. This flow rate was maintained until no supplemental oxygen was required, then decreased by 0.5 litres/min every 6 h to 0.5 litres/min. The HFNC group had a clinically important increase in days on oxygen (median 14 vs. 5 days; $p < 0.001$) and duration of respiratory support (18 vs. 10.5 days; $p = 0.03$).

Iranpour et al. [33] randomised preterm infants (30–35 weeks' gestation) 24 h after early surfactant treatment and immediate extubation to NCPAP to either continuing NCPAP at 6–8 cm H_2O or changing to Fisher & Paykel HFNC. Flow rates used in the HFNC group were determined from the formula of Sreenan et al. [28]. There were no differences between the groups with regard to short-term morbidities, duration of hospitalisation or duration of oxygen treatment.

How Safe Is HFNC for Preterm Infants?

The most widely publicised complication arising from HFNC use in preterm infants was the *Ralstonia* contamination of the Vapotherm system that forced a temporary recall of these units in 2005 [34]. The Vapotherm system has since been subject to more stringent infection control measures and is back in widespread use. There has also been a case report [35] of a preterm infant who was receiving humidified HFNC at 2 litres/min (device not reported) and concomitantly was found to have subcuta-

neous scalp emphysema and pneumo-orbitus, which resolved after discontinuation of the HFNC. The authors noted that these complications may have been a result of nasopharyngeal trauma rather than the mode of support.

Few studies have reported other adverse outcomes of importance to neonatal clinicians. In the RCT of Campbell et al. [13], no differences were noted in the incidence of necrotizing enterocolitis, intraventricular haemorrhage, BPD, sepsis or retinopathy of prematurity between the NCPAP and HFNC groups. There were no pneumothoraces in either group. Holleman-Duray et al. [7] found no differences in rates of pulmonary or extra-pulmonary side effects, death, oxygen use or length of admission, but infants in the HFNC era spent fewer days on the ventilator (mean 11.4 vs. 18.5 days; $p = 0.028$). Iranpour et al. [33] found no differences in rates of death, BPD, pneumothoraces, other short-term morbidities or duration of hospitalisation or oxygen therapy. Shoemaker et al. [6] and Nair and Karna [unpubl. data] also found no difference in rates of death or BPD.

HFNC are thought to be more comfortable for preterm infants and to cause less nasal septal trauma than NCPAP. Three studies have included nasal trauma as an outcome. In the study by Woodhead et al. [15] of humidifying HFNC, the noses of infants were examined by a blinded investigator 24 h after starting the modality; those on Vapotherm had more normal examinations of the nasal mucosa than did those on unhumidified high flow. Campbell et al. [13] used digital photography to score the nasal mucosa on days 1, 7 and 30 following extubation but did not observe any significant nasal damage in either group. Iranpour et al. [33] used a nasal trauma scoring system and reported that infants treated with HFNC had significantly less trauma than those on NCPAP.

Although the above results are reassuring, the limitations of these studies mean that the safety of HFNC in the preterm population has yet to be adequately demonstrated. Until larger randomised studies are complete, the safety of HFNC will not have been established.

Recommendations

Surveys show that HFNC is widely used to treat preterm infants, and there is growing evidence of its feasibility as an alternative to other forms of non-invasive ventilation. However, there remains uncertainty about the efficacy and safety of HFNC in this population, and there are no long-term outcome data.

If HFNC is to be used, we recommend only heated, humidified HFNC systems with flow rates ≥ 2 litres/min, up to the maximum flow rate recommended by the manufacturer. The use of improperly humidified gases may lead to drying of the airway mucosa and increase the risk of infection, as well as thick and dry secretions. Also, in our experience, the use of flow rates lower than 2 litres/min tends to increase the amount of condensation in the tubing. Prongs should be chosen so as not to completely occlude the nares. When setting the flow rate, the infant's weight must be considered as pressure generation increases with decreasing infant size. A starting flow rate of 4–6 litres/min in newly born preterm infants would seem like a reasonable balance between efficacy and safety based on the available evidence and current clinical practices, with infants < 1 kg starting at the lower end of that range.

Research should concentrate on the pragmatic questions of 'does it work?' and 'is it safe?' compared to the current gold standard non-invasive support, NCPAP. There is still the need to define effective and safe minimum and maximum flow rates for the preterm population. Several RCTs that are studying HFNC as post-extubation support and as a primary therapy for RDS are under way. Until the results of these trials are known, widespread use of HFNC to treat preterm infants cannot be recommended.

Disclosure Statement

None of the authors has a conflict of interest to declare.

Appendix (see next page)

Appendix. Details of clinical studies included in the review

Study	n	GA and weight	Study type and design	Devices, HFNC flow rates and HFNC prong sizes (outer diameter)	Outcomes	Key results	Comments	LOE
Iranpour et al. 2011 [33]	70	HFNC group: mean GA 32.3 weeks, BW 1.82 kg; NCPAP group: mean GA 32.5 weeks, BW 2.21 kg	RCT of NCPAP vs. HFNC as ongoing respiratory support after prophylactic surfactant and early extubation to NCPAP	HFNC F&P; flow rates determined by Sreenan's formula; prongs: 0.2 cm	outcomes included death, NEC, PDA, IVH, BPD, duration of oxygen therapy and time in hospital, nasal trauma	no differences in specified outcomes; HFNC group had more normal examinations of nasal mucosa	full text of article in Arabic, English abstract	1
Abdel-Hady et al. 2011 [32]	60	HFNC group: mean GA 31.1 weeks, BW 1,600 g; NCPAP group: mean GA 31.0 weeks, BW 1,600 g	RCT of weaning from NCPAP with/without weaning to heated, humidified HFNC	F&P water-seal NCPAP with binasal prongs; humidified HFNC; flow rate 0.5–2 litres/min; Ultramed prongs: 0.3 cm	duration of respiratory support, days on oxygen, LOS	the NCPAP-only group had fewer days on oxygen (median 5 vs. 14 days) and shorter duration of respiratory support (10.5 vs. 18 days); no differences between groups regarding success of weaning from NCPAP	used flow rates in the HFNC group of ≤ 2 litres/min	1
Miller and Dowd 2010 [14]	40	F&P group: mean GA 28.2 weeks, mean BW 1,078 g; Vapotherm group: mean GA 28.2 weeks, mean BW 1,100 g	RCT of Vapotherm 2000i HFNC vs. F&P HFNC	Vapotherm and F&P heated and humidified HFNC; flow rate 6 litres/min; F&P prongs: 0.24–0.27 cm; Vapotherm prongs: 0.25–0.28 cm	prevention of extubation failure within 72 h	no statistical differences but rate of extubation failure was 18% for F&P vs. 9% for Vapotherm	study funded by F&P and Vapotherm	1
Campbell et al. 2006 [13]	40	HFNC group: mean GA 27.4 weeks, BW 1,008 g; NCPAP group: mean GA 27.6 weeks, BW 925 g	RCT of unheated, humidified HFNC vs. NCPAP	Salter Labs HFNC, Infant Flow NCPAP; flow rates 1.4–1.7 litres/min; 'infant' size Salter prongs	prevention of extubation failure	significantly more HFNC infants required reintubation (12/20 vs. 3/20); HFNC group had increased oxygen use and more apnoeas and bradycardias after extubation	used much lower HFNC flow rates than in current clinical practice (mean 1.6 litres/min), predicted from Sreenan's formula	1
Nair and Karna 2005 [unpubl. data]	67	HFNC group: mean GA 32 weeks, BW 1,675 g; NCPAP group: mean GA 31 weeks, BW 1,493 g	RCT of HFNC vs. 'Bubble' NCPAP	Vapotherm 2000i HFNC, 'Bubble' constant-flow NCPAP; mean flow rates 5–6 litres/min; prong sizes unknown	primary treatment of RDS; respiratory failure was defined with blood gas parameters, apnoea or bradycardia	no statistical differences; Vapotherm appears to provide as effective respiratory support as NCPAP in the initial treatment of respiratory distress	trial ceased early	1
Lampland et al. 2009 [27]	15	mean GA 29.5 weeks, mean BW 1,324 g	observational study; heated and humidified HFNC vs. NCPAP	F&P RT329 HFNC, Draeger Babylog 8000 NCPAP; flow rates 1–6 litres/min; F&P 'neonatal' prongs (0.24 cm)	heart rate, RR, fraction of inspired oxygen, arterial oxygen saturation, 'RDS score'; oesophageal pressure monitoring	RR increased as flow rates decreased; other physiological parameters did not differ; pressure increases with increasing flow; high inter- and intra-patient variation in pressure	only one cannula size used	2

Appendix (continued)

Study	n	GA and weight	Study type and design	Devices, HFNC flow rates and HFNC prong sizes (outer diameter)	Outcomes	Key results	Comments	LOE
Kubicica et al. 2008 [26]	27	GA range 25–40 weeks, BW 605–3,657 g; PCA 29.1–44.7 weeks, study weight 835–3,735 g	observational study, heated and humidified HFNC	Vapotherm 2000i (n = 16) or F&P RT329 (n = 11) HFNC; flow rates 1–5 litres/min; 0.2-cm prongs	oral pressure monitoring	no pressure generated with mouth open; pressure increases with flow in infants <1,500 g with mouth closed	only one cannula size used; GA and BW much higher than in other studies	2
Wilkinson et al. 2008 [21]	18	median GA 27.1 weeks, median BW 944 g; median PCA 33.6 weeks, study weight 1,619 g	observational study, heated and humidified HFNC	F&P RT329 HFNC; flow rates 2–8 litres/min; F&P prongs: 'neonatal' 0.14 cm, 'infant' 0.19 cm, 'pediatric' 0.27 cm	pharyngeal pressure monitoring	pressure increases with increasing flow; mouth position is irrelevant; increasing weight, decreasing pressure	lower GA and BW than other studies; studied flow rates up to 8 litres/min; produced formula to predict pressure: $P (\text{cm H}_2\text{O}) = 2.6 + (0.8 \times \text{flow rate}) - (1.4 \times \text{infant weight})$	2
Boumeid et al. 2007 [20]	13	mean GA 29 weeks, mean BW 1,350 g	crossover study of continuous-/variable-flow NCPAP vs. unheated and unhumidified HFNC (randomly applied)	1. variable-flow NCPAP (Infant Flow) at 5 cm H ₂ O; 2. constant-flow NCPAP (Baby-Flow) at 5 cm H ₂ O; 3. HFNC; flow rate 2 litres/min; internal diameter of prongs: 0.15 cm	RIP; RR, V _t , thoraco-abdominal synchrony	variable-flow NCPAP: increase in tidal volume, improved thoraco-abdominal synchrony compared to other strategies; HFNC not different to constant-flow NCPAP	only studied HFNC at 2 litres/min	2
Spence et al. 2007 [25]	14	median study GA 30 weeks, median study weight 1,589 g	observational study, heated and humidified HFNC (n = 12) and NCPAP (n = 8)	F&P HFNC, Infant Flow NCPAP; flow rates 1–5 litres/min; 'infant' size Salter prongs	pharyngeal pressure monitoring	HFNC pressure increases with increasing flow	only used one size of cannula for all infants	2
Saslow et al. 2006 [30]	18	mean GA 28.2 weeks, mean BW 1,118 g; mean study weight 1,542 g	observational crossover study, heated and humidified HFNC vs. NCPAP	Vapotherm 2000i; HFNC, NCPAP Infant Bird Ventilator; flow rates 3–5 litres/min; HFNC prong size unknown	'lung mechanics': work of breathing, V _t (RIP), RR; oesophageal pressure monitoring	no difference in lung mechanics at any flow rate; pressures did not vary except at 5 litres/min	infants served as their own control	2
Woodhead et al. 2006 [15]	30	'standard' HFNC group: mean GA 32 weeks, BW 1,715 g; Vapotherm group: mean GA 31 weeks, BW 1,630 g	RCT, crossover design, unheated, unhumidified HFNC vs. heated and humidified HFNC	unknown 'standard' HFNC system, Vapotherm 2000i; heated and humidified HFNC; mean flow rate 3.1 litres/min (range unknown); Vapotherm 'prematüre', 'neonatal' or 'infant' prongs	prevention of extubation failure; RR and respiratory effort score; nasal examination	more patients failed extubation (7 vs. 0) in the 'standard' HFNC group; no difference in RR; Vapotherm group had lower nasal injury scores at 24 h and lower respiratory effort scores	infants served as their own control; current HFNC systems are heated and humidified, so comparator not relevant now	2

Appendix (continued)

Study	n	GA and weight	Study type and design	Devices, HFNC flow rates and HFNC prong sizes (outer diameter)	Outcomes	Key results	Comments	LOE
Greenan et al. 2001 [28]	40	mean GA 28.7 weeks; PCA at study 30.3 weeks; mean study weight 1,260 g	observational study, unheated, humidified HFNC vs. NCPAP	Salter Labs HFNC, Infant Star NCPAP; flow rates 1–2.5 litres/min; Salter Labs 'infant' size prongs	treatment of AOP; oesophageal pressure monitoring	no difference in frequency or duration of apnoeas; flow rate required to generate NCPAP of 6 cm H ₂ O increases with increasing infant weight	only one cannula size used; produced formula to predict flow required for pressure of 6 cm H ₂ O: flow rate = 0.92 + (0.68 × infant weight)	2
Locke et al. 1993 [19]	13	mean GA 30 weeks, mean BW 1,377 g	observational study, unheated and unhumidified HFNC	Salter Labs HFNC; flow rates 0.5–2 litres/min; 0.2- and 0.3-cm prongs	oesophageal pressure monitoring; ventilatory patterns with RIP	no pressure generation with smaller prongs at any flow rate; larger prongs deliver increasing pressure with increasing flow and reduced breathing asynchrony	mean pressure of 9.8 cm H ₂ O at 2 litres/min; unhumidified system	2
Holleman-Duray et al. 2007 [7]	114	HFNC group: mean GA 27.6 weeks, BW 1,060 g; NCPAP group: mean GA 27.4 weeks, BW 1,000 g	retrospective study, heated and humidified HFNC (n = 65) vs. NCPAP (n = 49); 'early extubation protocol' for infants of 25–29 weeks' GA	Vapotherm 2000i; HFNC, Sechrist Infant Ventilator NCPAP; extubated to flow rates of 4–6 litres/min; prong size unknown	included: incidence of extubation failure, PDA, IVH, PVL, NEC, sepsis, BPD at 28 days and 36 weeks, and death	no differences in major outcomes or oxygen use; HFNC group had lower ventilator rate at extubation (32.6 vs. 28) and fewer ventilator days (11.4 vs. 18.5)	retrospective study design	3
Shoemaker et al. 2007 [6]	101	era 1: mean GA 28.1 weeks, mean BW 1,050 g; era 2: mean GA 27.6 weeks, mean BW 1,017 g	retrospective, descriptive study, heated and humidified HFNC (n = 65) vs. NCPAP (n = 36)	Vapotherm HFNC, Arabella/Infant Star/Infant Flow NCPAP; flow rates 2.5–8 litres/min; internal diameter of prongs: 0.15 cm	primary treatment of RDS or prevention of extubation failure; outcome measures included: death, air leak, infection, BPD, NEC, PDA, IVH, ROP, LOS	HFNC 'well tolerated'; no differences in adverse outcomes following the introduction of HFNC; less extubation failure (18 vs. 40%) and days ventilated (9.9 vs. 19.4) with HFNC	retrospective study design	3

BW = Birth weight; F&P = Fisher & Paykel; GA = gestational age; IVH = intraventricular haemorrhage; LOE = level of evidence; LOS = length of stay; NEC = necrotising enterocolitis; PCA = post-conceptual age; PDA = patent ductus arteriosus; PVL = periventricular leukomalacia; RIP = respiratory inductive plethysmography; ROP = retinopathy of prematurity; RR = respiratory rate.

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