Heated Humidified High Flow Nasal Cannula Compared To Nasal Continuous Positive Airway Pressure for Neonates: A Systematic Review and Meta-analysis

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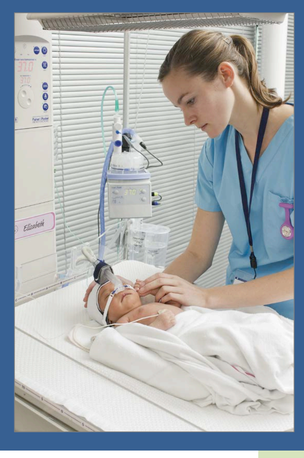

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Introduction

- Heated humidified high flow nasal cannula (HHHFNC) devices are being used as an alternative to nasal continuous positive airway pressure (nCPAP) to treat conditions such as respiratory distress syndrome, apnoea of prematurity and to prevent extubation failure[1].
- HHHFNC appears to be less invasive, tolerated better by infants[1] and allows for improved parent and infant interaction[2,3].
- The use of HHHFNC has increased and been proposed as an alternative to nCPAP but the safety and efficacy of this form of respiratory support in the neonatal population has not been established as routine practice[4].

Objective

To assess the safety and efficacy of HHHFNC as compared to nCPAP to provide non-invasive respiratory support for preterm and term neonates in the neonatal intensive care setting.

Figure 2. Flow diagram of study selection

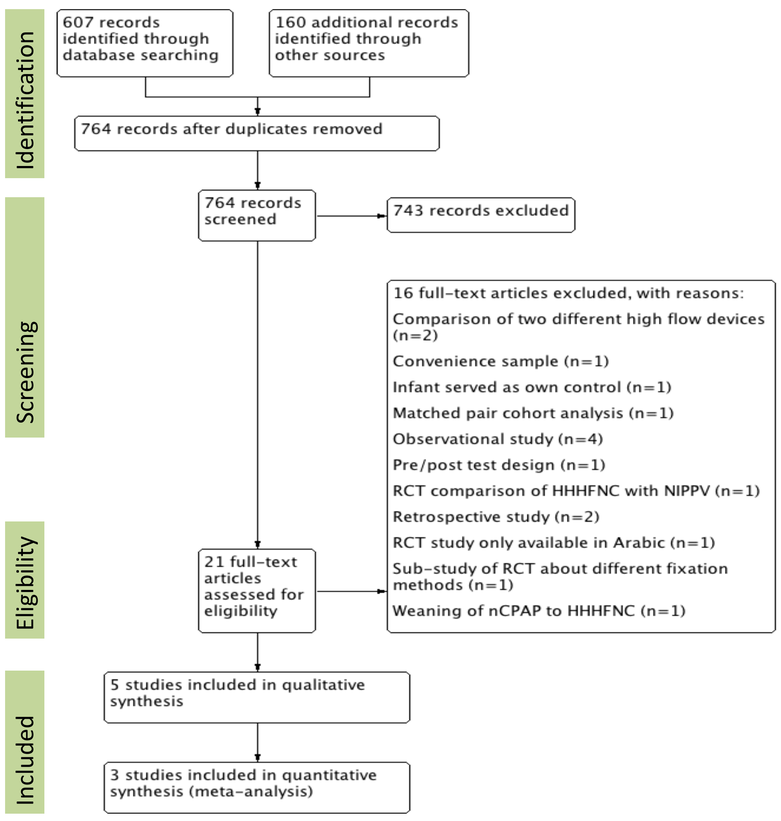


Figure 3. Forest plot of primary outcome: intubation within seven days of starting study mode

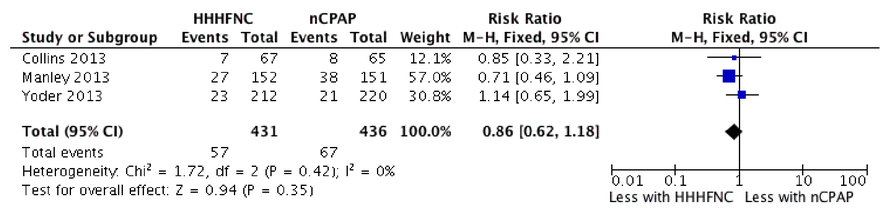


Figure 4. Forest plot of adverse event: necrotising enterocolitis

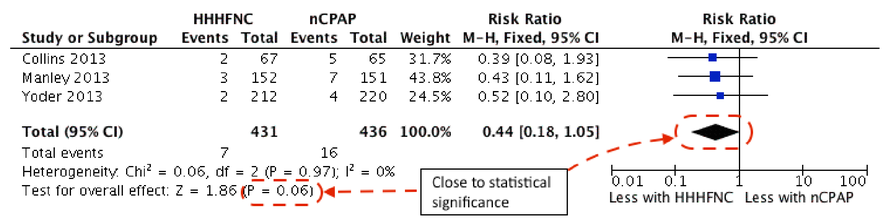
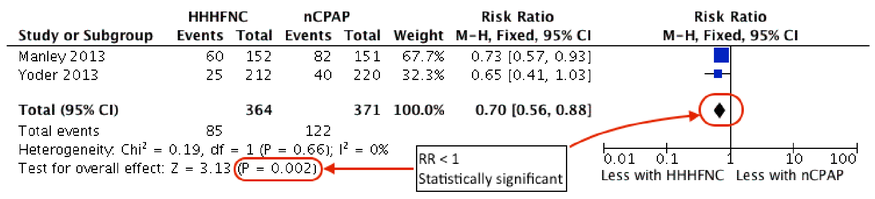


Figure 5. Forest plot of adverse event: nasal trauma



Methods

Databases searched: Cochrane Central Register of Controlled Trials (CENTRAL): Issue 3 of 12 March 2014 (The Cochrane Library), MEDLINE, EMBASE, PUBMED, CINAHL and SCOPUS, ClinicalTrials.gov, Australia New Zealand Clinical Trials Registry, and World Health Organization International Trials Registry Platform.

- Request made to Fisher & Paykel Healthcare Ltd. and Vapotherm Inc. for any known unpublished studies.
- An attempt was made to obtain results from an unpublished study[5] by Nair and Karna (2005) but was unsuccessful due to lack of contact details.

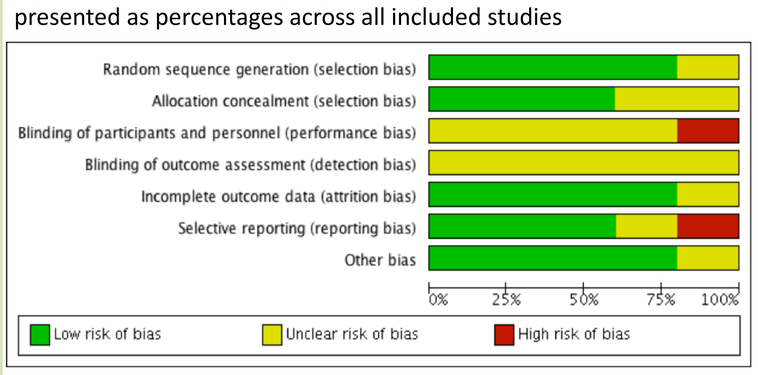
Selection criteria: Randomised controlled trials (RCT) comparing HHHFNC with nCPAP for neonates of any gestational age (preterm and term).

Data collection and analysis:

- Two reviewers (CP and FR) independently assessed each study for inclusion and extracted data from studies.
- Data collected by the author (CP) was recorded in a Microsoft Word document, using a layout based on the Cochrane handbook for systematic reviews of interventions[6] (version 5.1.0, checklist from table 7.3a).
- Extracted data was checked by the second reviewer (FR).
- Cochrane Collaboration methodological procedures were used.
- Review manager (RevMan version 5.2) software was used to analyse and present data as forest plots using fixed effect model.
- Risk ratios and p values were calculated. Results were considered significant if the p value was less than 0.05.
- Data entered into RevMan software was checked for accuracy by the second reviewer (FR).
- Studies excluded were those that were not available in English due to time and resource constraints.

Risk of Bias Summary

Figure 1: Review authors' judgments about each risk of bias item, presented as percentages across all included studies



Potential Conflicts of Interest

None known.

Results

- Five studies were selected for inclusion.
- Three studies [7,8,9] provided data that could be used in the meta-analysis : Collins 2013, Manley 2013, and Yoder 2013.
- Participants: Total of 867 from 12 different neonatal units in three countries (Australia, United States of America, and China)
  - Gestation of neonates ranged from < 26 weeks to 42 weeks
  - Gestation < 26 weeks n = 63
  - Gestation > 32 weeks n = 284
- No differences were seen when HHHFNC was compared to nCPAP for five outcomes: intubation at any time after study entry, intubation within seven days of starting study mode, chronic lung disease at 36 weeks postmenstrual age (PMA), days to reach full feeds, and infants discharged on home oxygen.
- No differences were seen when HHHFNC was compared to nCPAP for four adverse events: mortality, pulmonary air leak, intraventricular haemorrhage or necrotising enterocolitis.
- However, there was 30% lower risk of nasal trauma with HHHFNC compared to nCPAP (RR: 0.70: 95%CI: 0.56 to 0.88; p = 0.002)

Table 1. Characteristics of included studies.

Studies for meta-analysis	Collins 2013 (N = 132) HHHFNC n = 67 nCPAP n = 65	Manley 2013 (N = 303) HHHFNC n = 152 nCPAP n = 151	Yoder 2013 (N = 432) HHHFNC n = 212 nCPAP n = 220
Trial	RCT Single site NICU Melbourne, Australia Study duration 7 days Follow up until discharge	Randomised non-inferiority trial Multisite NICU's Adelaide, Melbourne, Brisbane (Australia) Study duration 7 days Follow up until discharge	RCT Multisite NICU's U.S.A (7) China (1) Study duration 72 hours Follow up until discharge
Eligibility criteria	Born < 32 weeks PMA Required intubation & positive pressure ventilation(PPV) and ready for extubation	Born < 32 weeks PMA Required intubation & PPV and ready for extubation	Birth weight ≥ 1000g & GA ≥ 28 weeks Planned CPAP either as primary support or post extubation
Mean gestational age in weeks (SD)	HHHFNC: 27.9 (1.95) nCPAP: 27.6 (1.97)	HHHFNC: 27.7 (2.1) nCPAP: 27.5 (1.0)	HHHFNC: 33.5 (3.6) nCPAP: 33.2 (3.2)
Mean birth weight, grams (SD)	HHHFNC: 1123 (317) nCPAP: 1105 (374)	HHHFNC: 1041 (338) nCPAP: 1044 (327)	HHHFNC: 2201 (826) nCPAP: 2108 (782)
HHHFNC device and flows	Vapotherm™, started on flow 8 l/min Flow range 4 – 8 l/min	Optiflow™, starting flows depended on nasal prong size. Premature 5–6 l/min, neonatal 6–7 l/min, peadiatric 6–8 l/min	ComfortFlo®, Fisher & Paykel Healthcare and Vapotherm™ Flow range 2–8 l/min
nCPAP device and PEEP	Device not reported. If FiO_2 > 0.3 started on PEEP 8 cm H_2O If FiO_2 < 0.3 started on PEEP 7 cm H_2O	Bi-nasal midline or subnasal prongs via underwater bubble system or ventilator Started on PEEP 7 cm H_2O	Bubble, Infant Flow®nCPAP system, and ventilator PEEP range 5-8 cm H_2O

Discussion

- Quality of evidence for each outcome assessed using the GRADE approach and randomised trials are considered to have the highest rating[10].
- GRADE approach indicated the three studies [7,8,9] used in the meta-analysis are methodologically sound. (Summaries of findings tables using GRADE approach not shown on poster)
- The 867 neonates in the studies had a range of gestations from < 26 weeks to 42 weeks with most at gestations of 26 to 32 weeks (n = 520)
- Non-invasive respiratory support was used for different indications in the studies (post extubation support, respiratory distress syndrome and apnoea of prematurity) which reflects the indications for nCPAP in neonatal units.
- A range of devices were used for HHHFNC and nCPAP:
  - Flow rates for HHHFNC ranged from 2 to 8 l/min
  - nCPAP pressures ranged from 4 to 8 cm H_2O.
- The only statistical difference found was with nasal trauma showing fewer neonates developing this problem in the HHHFNC group compared to nCPAP group and likely related to smaller sized prongs with a 50% leak at the nares which is needed for high flow to be effective.

Conclusions

- This review has external validity and can be applied to neonates in neonatal intensive care units and non-tertiary neonatal care units.
- The review found that HHHFNC at flows of 2 to 8 l/min can be used with similar efficacy and safety as nCPAP pressures of 4 to 8 cm H_2O in the outcomes listed in this review.
- Due to HHHFNC being a less invasive procedure, better tolerated by infants (including improved parent-infant interaction), and with significantly less nasal trauma, it is hoped the use of HHHFNC will be considered the first line option for non-invasive respiratory support in neonatal settings.

Implications for Practice and Research

- This review has shown no clinically meaningful difference between HHHFNC and nCPAP in the neonatal population.
- Treatment failure rates for neonates < 26weeks gestation were found to be higher in the HHHFNC group compared to nCPAP group in the Manley 2013 study
- Authors from the Collins 2013 and Yoder 2013 studies suggested more RCT's are needed for neonates < 28 weeks gestation
- One study (Yoder 2013) involved neonates over 32 weeks gestation. These neonates are at risk for respiratory distress syndrome, transient tachypnea of the newborn and meconium aspiration syndrome thus RCT's comparing HHHFNC to nCPAP for these older neonates would be beneficial.

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References

1. Dani C, Pratesi S, Migliori C, Bertini G. (2009) High flow nasal cannula therapy as respiratory support in the preterm infant. *Pediatric Pulmonology*. 2009, **44**, 629 - 634
2. Hough JL, Shearman AD, Jardine LA, Davies MW. (2012) Humidified high flow nasal cannulae: current practice in Australasian nurseries, a survey. *Journal of Paediatrics and Child Health.* February 2012, **48**(2), 106 – 113.
3. Ojha S, Gridley E, Dorling J. (2013). Use of heated humidified high-flow nasal cannula oxygen in neonates: a U.K wide survey. *Acta Paediatrica*
4. DiFiore JM, Martin R J, Gauda EB. (2013). Apnea of prematurity – perfect storm. *Respiratory Physiology & Neurobiology.*2013, **189,** 213 -222
5. Nair G, Karna P. (2005). Comparison of the effects of Vapotherm and nasal CPAP in respiratory distress. *Peadiatric Academic Societies* 2005; 1 Unpublished
6. Higgins, J P T, Thompson SG. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*. 2002. **21**, 1539 - 1558
7. Collins C L, Holberton J R, Barfield C, Davis PG. (2013). A randomised controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. *The Journal of Pediatrics*. May 2013, **162**(5), 949 – 954
8. Manley B J, Owen L S, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA, Donath SM, Davis PG. (2013) High-flow nasal cannulae in very preterm infants after extubation. *The New England Journal of Medicine.* October 10, 2013, **369**(15), 1425 – 1433.
9. Yoder BA, Stoddard RA, Li M, King J, Dirnberger DR, Abbasi S. (2013). Heated, humidified high-flow nasal cannula versus nasal CPAP for respiratory support in neonates. Pediatrics. May 2013, **131**(5), 1482 – 1490.
10. Higgens JPT, Green S. (2011) Cochrane Handbook for systematic reviews of interventions version 5.1.0. *The Cochrane Collaboration, updated March 2011*