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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 3
OBJECTIVES 3
METHODS 3
RESULTS 6
DISCUSSION 6
AUTHORS' CONCLUSIONS 7
ACKNOWLEDGEMENTS 7
REFERENCES 8
WHAT'S NEW 9
CONTRIBUTIONS OF AUTHORS 9
DECLARATIONS OF INTEREST 9
SOURCES OF SUPPORT 9
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 9
INDEX TERMS 9

[Intervention Review]

Strategies for the discontinuation of humidified high flow nasal cannula (HHFNC) in preterm infants

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ABSTRACT

Background

Humidified high flow nasal cannula (HHFNC) delivers humidified gas at increased flow rates via binasal prongs and is becoming widely accepted as a method of non-invasive respiratory support for preterm infants. While indications for the use of (HHFNC) and its associated risks and benefits are being investigated, the best strategy for the discontinuation of HHFNC remains unknown. At what point an infant is considered stable enough to attempt to start withdrawing their HHFNC is not known. The criteria for a failed attempt at HHFNC discontinuation is also unclear.

Objectives

To determine the risks and benefits of different strategies used for the discontinuation of HHFNC in preterm infants.

Search methods

We searched the Cochrane Neonatal Review Group Specialized Register, PubMed (1966 to March 2015), CINAHL (1982 to March 2015), EMBASE (1980 to March 2015), and the Cochrane Central Register of Controlled Trials (CENTRAL). Also, we checked previous reviews, including cross references. We searched for following web sites for ongoing trials: ClinicalTrials.gov and controlled-trials.com.

Selection criteria

We included randomised controlled trials (RCTs) and quasi-RCTs in which either individual newborn infants or clusters of infants (such as separate neonatal units) were randomised to different HHFNC withdrawal strategies (from the first time they come off HHFNC and any subsequent weaning, or withdrawal attempt, or both).

Data collection and analysis

We used standard methods of Cochrane and the Cochrane Neonatal Review Group.

Main results

We identified no eligible studies examining the best strategy to wean or withdraw HHFNC once started as respiratory support in preterm infants

Authors' conclusions

There is currently no evidence available to suggest the best strategy for weaning and withdrawing HHFNC as a respiratory support in preterm infants. Research is required into the best strategy for withdrawal of HHFNC and to which subgroups this applies. Clear criteria for the definition of stability prior to attempting to withdraw HHFNC needs to be established. Furthermore, clear definitions are needed as to what constitutes failure of HHFNC.

PLAIN LANGUAGE SUMMARY

Strategies used for the withdrawal of humidified high flow nasal cannulae (HHFNC) in preterm infants

Background: Humidified high flow nasal cannula (HHFNC) is a form of respiratory support used in the treatment of preterm infants. Potential risks of HHFNC include damage to the nose and leaking of air from the lungs. Infants on HHFNC require more nursing care and the use of extra equipment (when compared to not being on any support). However, potential complications of removing HHFNC from babies too early include increased episodes of forgetting to breathe, increased oxygen needs, increased effort of breathing, the need to restart HHFNC, and the need for a breathing tube with mechanical ventilation. Any of these complications can be seen as a "failure" and are potentially distressing to staff and family. The best way to withdraw HHFNC once it has been started is unknown. Options include simply stopping, weaning the flow, increasing the time off HHFNC each day, or combinations of both.

Study question : What are the benefits and risks of different strategies used for the withdrawal of HHFNC in preterm infants who are stable and may be ready to have HHFNC withdrawn?

Study characteristics and key findings: Researchers from Cochrane searched for all available literature up to 30 March 2015. We did not identify any eligible studies looking at the best strategy to wean or withdraw HHFNC once started as respiratory support in preterm infants for inclusion in this Cochrane review.

Conclusions: The best strategy for weaning, or withdrawal, or both, of HHFNC used as a form of respiratory support in preterm infants remains unclear. Studies are required to answer these questions. Clear criteria are needed to establish a definition of stability prior to attempting to withdraw HHFNC, and for failure to withdraw/wean HHFNC.

BACKGROUND

Description of the condition

Humidified high flow nasal cannula (HHFNC) delivers humidified gas at increased flow rates via binasal prongs. The definition of 'high flow' varies; in a recent Cochrane review, Wilkinson 2011 defined high flow as greater than 1 L/min, whereas others have suggested that HHFNC is when flow rates are greater than 2 L/min (Manley 2012a). HHFNC is becoming widely accepted as a method of non-invasive respiratory support within neonatal intensive care nurseries and non-tertiary nurseries (Holleman-Duray 2007; Shoemaker 2007; Hochwald 2010; Nath 2010; Hough 2012; Manley 2012b). Clinical situations in which HHFNC is being used include primary respiratory therapy for infants with respiratory distress syndrome (RDS), apnoea of prematurity (AOP), prevention of extubation failure, and weaning from nasal continuous positive airway pressure (NCPAP) (Abdel-Hady 2011; Iranpour 2011; Manley 2012a). This comes despite ongoing concerns over both its safety and efficacy in the neonatal population, with a Cochrane review examining the risks and benefits (Wilkinson 2011) of HHFNC concluding that insufficient evidence exists to determine its use as a form of respiratory support in preterm infants.

Description of the intervention

While continued investigations are attempting to determine both the optimal technique of HHFNC delivery and the clinical setting in which it is most useful, the best strategy for the stopping or weaning of HHFNC remains unknown. At what point an infant is considered stable enough to attempt to start withdrawing their HHFNC is not clearly established. The criteria for a failed attempt at HHFNC withdrawal are unclear. A recent study looked at possible methods for weaning NCPAP in preterm infants (Todd 2012). Clearly defined criteria for stability prior to weaning, and for failing once off CPAP, were given. Whether these criteria are applicable to HHFNC is unknown, and requires investigation.

Possible strategies for the withdrawal of HHFNC include:

1. Stopping HHFNC completely, independent of the level of air flow, and remaining off HHFNC unless certain criteria are met that require the infant to go back onto HHFNC;
2. Decreasing HHFNC to a predefined flow, then stopping HHFNC completely;
3. Removing HHFNC for a predetermined number of hours each day (this can be a single time period: e.g. 4 hours off, 20 hours on; or a number of smaller time periods e.g. one hour off, five hours on), gradually increasing the amount of time off HHFNC each day until HHFNC is able to be stopped completely (graded time off);
4. Stopping HHFNC and starting low flow oxygen via a nasal cannula;
5. Combinations of the above strategies (e.g. decreasing HHFNC to a defined flow and then discontinuing HHFNC for a number of hours each day);
6. Combinations of the above strategies in addition to co-interventions (e.g. methylxanthines).

How the intervention might work

The possible benefits of different methods of HHFNC withdrawal are unknown. Weaning the flow rate may gradually increase respiratory muscle strength without the associated risk of atelectasis. Having periods of time off may have a similar effect of respiratory muscle training, but for shorter, more intense periods. Time off HHFNC may be more likely to cause 'atelectotrauma' (due to alveolar collapse when off HHFNC and re-recruitment once HHFNC recommences). Having periods of time off HHFNC may reduce the risk of developing adverse effects, given reports that its use may lead to mucosal irritation, nasal bleeding, and obstruction (Kopelman 2003). An appropriate weaning strategy may alleviate any concerns of lung overdistension from unmeasured positive end-expiratory pressure (PEEP) (Finer 2009), and any other possible risks (Wilkinson 2011).

Why it is important to do this review

HHFNC is being used in increasing frequency in neonatal units, despite ongoing concerns over its safety and efficacy. While a number of trials are underway to determine the best role for HHFNC in respiratory support of neonates, there are a number of reported strategies as to how to cease HHFNC once it has been commenced. It is unknown as to the best strategy for withdrawal and to what patient groups this should apply. This review complements the Cochrane review on "Strategies for the withdrawal of nasal continuous positive airway pressure in preterm infants" (Jardine 2011).

OBJECTIVES

To determine the benefits and harms of different strategies for the withdrawal of HHFNC in preterm infants who are stable and may be ready to have HHFNC withdrawn.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all eligible randomised controlled trials (RCTs) and quasi-RCTs in which either individual newborn infants or clusters of infants (such as separate neonatal units) were randomised to different HHFNC withdrawal strategies (from the first time they come off HHFNC and any subsequent weaning, or withdrawal attempt, or both).

Types of participants

Spontaneously breathing preterm infants (< 37 weeks completed gestational age) currently receiving respiratory support via HHFNC for any indication, who remain inpatients, and for whom the decision had been made to attempt discontinuation/withdrawal of respiratory support. We excluded infants in whom the decision to discontinue respiratory support was taken as part of withdrawing life-sustaining therapy. Participants should have met criteria for stability (however defined in individual studies) prior to their first attempt at withdrawal. We planned to exclude trials that did not include criteria for stability.

Types of interventions

Any strategy that involved the stopping or gradual withdrawal of HHFNC (> 1 L/minute). Strategies include:

1. Stopping HHFNC completely, independent of the level of air flow, and remaining off HHFNC unless certain criteria are met that require the infant to go back onto HHFNC;

2. Decreasing HHFNC to a predefined flow, then stopping HHFNC completely;
3. Removing HHFNC for a predetermined number of hours each day (this can be a single time period: e.g. 4 hours off, 20 hours on; or a number of smaller time periods e.g. one hour off, five hours on), gradually increasing the amount of time off HHFNC each day until HHFNC is able to be stopped completely (graded time off);
4. Stopping HHFNC and starting low flow air (and oxygen if required) via a nasal cannula;
5. Combinations of the above strategies (e.g. decreasing HHFNC to a defined flow and then discontinuing HHFNC for a number of hours each day);
6. Combinations of the above strategies in addition to co-interventions (e.g. methylxanthines).

Types of outcome measures

We planned intention-to-treat (ITT) analysis based on the first assigned method of withdrawal.

Primary outcomes

- Time (from treatment group allocation) to successfully remaining off HHFNC altogether (hours, days);
- Failure to wean off HHFNC (e.g. needing to restart HHFNC once it has stopped, or needing to restart HHFNC during time off HHFNC, or delaying any further weaning off HHFNC, or needing to commence/return to NCPAP or ventilation), however defined in individual studies.

Secondary outcomes

- Duration of HHFNC from initial intervention (days);
- Total duration of all respiratory support (i.e. any form of mechanical ventilation or NCPAP or HHFNC);
- Duration of hospital stay (days);
- Endotracheal intubation and mechanical ventilation, excluding episodes required for elective procedures (e.g. surgery);
- Incidence of air leak (any, and those requiring drainage) from time of treatment group allocation;
- Apnoea (defined as cessation of breathing > 20 seconds or > 10 seconds with desaturation, or however defined in individual studies);
- Nasal trauma including nasal bleeding;
- Duration of oxygen therapy (days);
- Chronic lung disease (oxygen requirement at 36 weeks postmenstrual age);
- Mortality (< 28 days);
- Mortality (at hospital discharge);
- Mortality (at one year);
- Long-term major neurodevelopmental disability (CP, developmental delay (Bayley or Griffith assessment more than two standard deviations (SD) below the mean) or intellectual impairment (intelligence quotient (IQ) more than two SD below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification). We planned to report long-term outcomes for all studies that evaluated children after 18 months' chronological age. We planned to perform separate analyses for children aged 18 to 24 months and over three years;
- Any other clinically-relevant outcomes identified in individual studies.

Search methods for identification of studies

Electronic searches

We used the standard search strategy for the Cochrane Neonatal Review Group. We searched the Cochrane Neonatal Review Group Specialised Register, CENTRAL (2015, Issue 3), PubMed (1966 to March 2015), EMBASE (1980 to March 2015), and CINAHL (1982 to March 2015), using the following strategy:

The text words "humidified high flow nasal cannula", "humidified high flow nasal cannulae", "humidified high-flow nasal cannulae", "high flow nasal cannula", "high-flow nasal cannula
AND
MeSH search term "Infant, Premature" OR the text words "neonat $", "infant", "preterm", "newborn", "premature".
AND
MeSH search term "Ventilator Weaning" OR text words "ceasing", "cessation", "wean", "weaning", "stop", "stopping", "withdraw$", "discontin$", "taper$".

We did not restrict searches to publications in the English language.

Searching other resources

We searched previous reviews (including cross references) without restricting searches to publications in the English language or to published data. In addition, we checked the following websites for ongoing trials: clinicaltrials.gov and controlled-trials.com.

We searched for abstracts from the Pediatric Academic Societies' Annual Meeting (Abstract2view) online 2000 to 2014.

Data collection and analysis

We planned to use the standard methods of Cochrane and the Cochrane Neonatal Review Group. We analysed only studies that allocated subsequent withdrawal attempts to the policy originally allocated.

Selection of studies

Two review authors independently screened trials for inclusion.

Data extraction and management

Review authors extracted data independently and resolved differences by discussion. We planned to contact study investigators for additional information or data as required. Also we planned to collect predefined outcome measures with the aid of a data collection form.

Assessment of risk of bias in included studies

Two review authors planned to independently assess trials for methodological quality. We planned to evaluate the following issues and enter the findings into the 'Risk of bias' tables (Higgins 2011):

1. Sequence generation (checking for possible selection bias): For each included study, we planned to categorise the method used to generate the allocation sequence as:
   a. Low risk (any truly random process e.g. random number table; computer random number generator);

b. High risk (any non random process e.g. odd or even date of birth; hospital or clinic record number);
c. Unclear risk.

2. Allocation concealment (checking for possible selection bias): For each included study, we planned to categorise the method used to conceal the allocation sequence as:
   a. Low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
   b. High risk (open random allocation; unsealed or non-opaque envelopes; alternation; date of birth);
   c. Unclear risk.
3. Blinding (checking for possible performance bias): For each included study, we planned to categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We planned to categorise blinding separately for different outcomes or classes of outcomes. We planned to categorise the methods as:
   a. Low risk, high risk, or unclear risk for participants;
   b. Low risk, high risk, or unclear risk for personnel;
   c. Low risk, high risk, or unclear risk for outcome assessors.
4. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations): For each included study and for each outcome, we planned to describe the completeness of data including attrition and exclusions from the analysis. We planned to note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we planned to re-include missing data in the analyses. We planned to categorise the methods as:
   a. Low risk (< 20% missing data);
   b. High risk (≥ 20% missing data);
   c. Unclear risk.
5. Selective reporting bias: For each included study, we planned to describe how we investigated the possibility of selective outcome reporting bias and what we found. We planned to assess the methods as:
   a. Low risk (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
   b. High risk (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
   c. Unclear risk.
6. Other sources of bias: For each included study, we planned to describe any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We planned to assess whether each study was free of other problems that could put it at risk of bias as:
   a. Low risk;
   b. High risk;
   c. Unclear risk.

Measures of treatment effect

We planned to perform statistical analyses using RevMan 2014 software. We planned to analyse categorical data using relative risk (RR), absolute risk difference (RD) and number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH). We planned to analyse continuous data using mean difference (MD) and report the 95% confidence interval (CI) on all estimates.

Unit of analysis issues

We planned to include cluster-RCTs in this Cochrane review and to confirm that the order of treatments had been randomised (Higgins 2002). We planned to attempt to access paired and unpaired data (Higgins 2002) and to impute the correlation coefficient from data provided in the included studies in this meta-analysis. If this was not available, we planned to assume a value of 0.4 and conduct a sensitivity analysis by successively using r = 0.3 and 0.5.

Dealing with missing data

We planned to attempt to contact trial authors for missing data. We planned to perform an ITT analysis based on the assigned method of withdrawal.

Assessment of heterogeneity

If a sufficient number of studies met the inclusion criteria, we planned to assess heterogeneity using the I^2 statistic and the following cutoffs: < 25% no heterogeneity; 25% to 49% low heterogeneity; 50% to 74% moderate heterogeneity; and ≥ 75% high heterogeneity. If we identified statistical heterogeneity, we planned to look for an explanation for this heterogeneity.

Assessment of reporting biases

In order to determine if there might be selective reporting, we planned to look for pre-specified outcomes in trial registries and compare these to reported outcomes. If there were discrepancies, we planned to attempt to contact the corresponding trial author.

In examining for duplication bias, we closely examined articles from repeated authors or sites and compare sample size, characteristics, and details of studies. If there appeared to be overlap, we planned to attempt to contact the corresponding trial author.

If we were not successful in contacting authors, we planned to included the possible sources of reporting bias in our conclusions.

To test for publication bias, we planned to perform a forest plot if there were ≥ 10 studies included in a meta-analysis.

We planned to examine the range of languages, location, and citation sources to examine potential bias.

Data synthesis

For the meta-analysis we planned to report MD and 95% CI for continuous variables. For the categorical outcomes we planned to report the RR, RD, and 95% CIs. When RD was statistically significant, NNTB and NNTH were planned to be examined.

We planned to use the fixed-effect model for meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses in an attempt to determine whether results differed by:

1. Gestational age at birth (e.g. < 29 weeks, ≥ 29 weeks);
2. Birth weight (e.g. < 1000 gm, ≥ 1000 gm);
3. Postnatal age (e.g. < four weeks of age, ≥ four weeks of age);
4. Indication for HHFNC (e.g. respiratory distress, post extubation, apnoea, chronic lung disease);
5. Delivery method of HHFNC (e.g. single prong versus binasal prong, bubble bottles versus ventilator);
6. Delivery device of HHFNC (e.g. Vapotherm or Fisher & Paykel).

Sensitivity analysis

We planned to perform a sensitivity analysis (data permitting) to see if results differed by the quality of included studies (e.g. adequacy of randomisation: quasi-RCT versus RCT).

RESULTS

Description of studies

Results of the search

Using the search strategy detailed above, we identified a number of studies for inclusion. However, after screening, no studies were eligible for inclusion. None of the studies we found included methods for weaning HHFNC, with most looking at comparisons between HHFNC and NCPAP.

Included studies

No studies met the inclusion criteria.

Excluded studies

None

Risk of bias in included studies

Not applicable.

Allocation

Not applicable.

Blinding

Not applicable.

Incomplete outcome data

Not applicable.

Selective reporting

Not applicable.

Other potential sources of bias

Not applicable.

Effects of interventions

Not applicable.

DISCUSSION

The evidence to support the use of HHFNC is evolving. Wilkinson 2011 identified four studies for inclusion in a Cochrane review of high flow nasal cannula (HFNC). The studies differed in the interventions compared (nasal CPAP, HHFNC, non-humidified HFNC), the flow rates provided, and the indications for respiratory support. Wilkinson 2011 concluded that there was insufficient evidence to determine the risks and benefits of using HHFNC as a form of respiratory support in preterm infants.

Since Wilkinson 2011, several larger trials of heated HHFNC have been reported. Yoder 2013 performed a randomised controlled unblinded non-crossover trial in 432 infants ranging from 28 to 42 weeks' gestational age with planned nasal CPAP support, as either primary therapy or postextubation. There was no difference in early failure (HHFNC 10.8% vs. nasal CPAP 8.2%; P = 0.344), subsequent need for any intubation (HHHFNC 15.1% vs. nasal CPAP 11.4%; P = 0.252), or in any of several adverse outcomes analysed including days on supplemental oxygen, bronchopulmonary dysplasia, or discharge from the hospital on oxygen.

Manley 2013 performed a multicentre, randomised, non-inferiority trial comparing HHFNC (5 to 6 L/minute) or nasal CPAP (7 cm H_2O) after extubation in 303 infants studies. HHFNC use was non-inferior to nasal CPAP use, with treatment failure occurring in 34.2% of infants in the nasal-cannula group and 25.8% of infants in the CPAP group (risk difference 8.4%, 95% CI -1.9 to 18.7%). The incidence of nasal trauma was significantly lower in the nasal cannula group than in the CPAP group (P = 0.01), but there were no significant differences in rates of serious adverse events or other complications.

HHFNC has come into widespread use in neonatal intensive care units, with over half of very low birthweight infants treated with HHHFNC at some point in their intensive care stay (Soll 2013). However, in our Cochrane review, we did not identify any studies providing information on the best method of weaning HHFNC in preterm infants who are stable and may be ready to have HHFNC withdrawn.

Research is required into the best methods for withdrawal of HHFNC and to which subgroups these apply. Clear criteria for the definition of stability prior to attempting to withdraw HHFNC needs to be established. Furthermore, clear definitions should be established as to what constitutes failure of HHFNC. A recent study (Todd 2012) looked at possible methods for weaning NCPAP in preterm infants. Clearly defined criteria for stability prior to weaning, and for failing once off CPAP, were given. Whether these criteria are applicable to HHFNC is unknown, and requires investigation.

Summary of main results

Not applicable.

Overall completeness and applicability of evidence

Not applicable.

Quality of the evidence

Not applicable.

Potential biases in the review process

Not applicable.

Agreements and disagreements with other studies or reviews

Not applicable.

AUTHORS' CONCLUSIONS

Implications for practice

There is no currently available evidence to suggest the best strategy for weaning and withdrawing HHFNC as a respiratory support in preterm infants.

Implications for research

Research is required into the best methods for withdrawal of HHFNC and to which subgroups these apply. Clear criteria for the definition of stability prior to attempting to withdraw HHFNC needs to be established. Furthermore, clear definitions should be established as to what constitutes failure of HHFNC.

ACKNOWLEDGEMENTS

None.

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WHAT'S NEW

Date	Event	Description
23 June 2015	Amended	Author affiliation update.

CONTRIBUTIONS OF AUTHORS

RCF and LAJ conceived the review and performed the literature searches.
RCF wrote the review.
LAJ, RCF and JLH revised the review.

DECLARATIONS OF INTEREST

LAJ is a co-investigator in Todd 2012

RCF has no known conflicts of interest to declare

JLH has no known conflicts of interest to declare

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added a more precise definition of "long-term major neurodevelopmental disability" (CP, developmental delay (Bayley or Griffith assessment > two SDs below the mean) or intellectual impairment (intelligence quotient (IQ) > two SDs below mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification). Long-term outcomes will be reported for all studies that have evaluated children after 18 months' chronological age. We will perform separate analyses for children aged 18 to 24 months and over three years.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Premature; Continuous Positive Airway Pressure [*methods]; Device Removal [adverse effects] [*methods]; Humidifiers; Noninvasive Ventilation [*methods]; Ventilator Weaning [adverse effects] [*methods]

MeSH check words

Humans; Infant, Newborn