Safety and Efficacy of High-Flow Nasal Cannula Therapy in Preterm Infants: A Meta-analysis

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Abstract

**Background and Objective:** High-flow therapy is the most recent, and popular, mode of respiratory support in neonates. However, the evidence supporting its efficacy and safety has not yet been established. We conducted a systematic review and meta-analysis of clinical trials comparing efficacy and safety of high-flow therapy compared with other modes of noninvasive ventilation (NIV) in preterm infants.

**Methods:** Articles were indexed by using Medline, Embase, Scopus, OpenSIGLE, Health Management Information Consortium, and Cochrane Central Register of Controlled Trials. Randomized or quasi-randomized clinical trials involving preterm infants, comparing high-flow therapy with other modes of NIV, and reporting extractable data on relevant outcomes, were selected. Data on efficacy, safety, and other common neonatal outcomes were extracted on predesigned forms.

**Results:** In this analysis, we included 1112 preterm infants, participating in 9 clinical trials. High-flow therapy was similar in efficacy to other modes of NIV in preterm infants when used as primary support (odds ratio of failure of therapy, 1.02 [95% confidence interval: 0.55 to 1.88]), as well as after extubation (1.09 [0.58 to 2.02]). There were no significant differences in odds of death (0.48 [0.18 to 1.24]) between the groups. Preterm infants supported on high-flow had significantly lower odds of nasal trauma (0.13 [0.02 to 0.69]).

**Conclusions:** High-flow therapy appears to be similar in efficacy and safety to other conventional modes of NIV in preterm infants. It is associated with significantly lower odds of nasal trauma. Caution needs to be exercised in extreme preterm infants because of the paucity of published data.

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Ms Kotecha designed the search strategy and ran the searches, collected and analyzed data, and reviewed and revised the manuscript; Dr Adappa and Dr Gupta shortlisted articles and reviewed and revised the manuscript; Dr Watkins undertook statistical analysis and reviewed and revised the manuscript; Professor Kotecha supervised searches, data collection and analysis, and critically reviewed the manuscript; Dr Chakraborty conceptualized and designed the study, supervised searches, shortlisted articles, supervised data analysis, and drafted the initial manuscript; and all authors approved the final manuscript as submitted.

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Respiratory failure, requiring invasive support with mechanical ventilation (MV) or noninvasive support with nasal modes of ventilation, remains the most common morbidity of preterm infants after birth. Recent studies suggest increased rates of survival of extreme preterm infants, with greater numbers needing respiratory support. Traditionally, this support has been in the form of invasive (through an endo-tracheal tube) MV. More recently, randomized controlled clinical trials have established the benefits of primary noninvasive ventilation (NIV) support, especially for nasal continuous positive airway pressure (nCPAP) when compared with MV. After extubation from MV, nCPAP is already established as an effective mode of support. Other modes of NIV in preterm infants include bilevel nCPAP (BiPAP)/noninvasive positive pressure ventilation (NIPPV) and heated humidified high-flow nasal cannula (HHHFNC) therapy. The use of BiPAP/NIPPV as a primary mode of respiratory support seems to be equally efficacious, and clinically superior after extubation from MV, when compared with nCPAP.

The most recent mode of respiratory support to be introduced for newborn infants, HHHFNC, however, has quickly gained popularity among clinicians worldwide, although evidence supporting its use is not fully established. Several clinical trials over the last decade have collected evidence of the use of HHHFNC in preterm infants, both as a primary mode of support at birth and after extubation from MV. We conducted a systematic review and meta-analysis to collect all published information, to be able to guide clinical practice.

**METHODS**

**Objectives**

Our objective was to assess the efficacy and safety of HHHFNC as respiratory support for preterm infants (<37 weeks’ gestational age [GA] at birth), when compared with other modes of NIV including nCPAP, and NIPPV or BiPAP.

**Inclusion Criteria**

We included prospective, randomized or quasi randomized controlled trials involving preterm infants born at <37 weeks’ GA. Trials involving mixed groups of infants (both preterm and term) were included if separate data for preterm infants were available (reported in the text, extracted from the data, or obtained from authors). No trials were excluded based on diagnosis of disease condition in the infants. Subgroups analyses were planned prospectively for <32 weeks’ GA (≤1500 g birth weight [BW]) and <28 weeks’ GA (≤1000 g BW), if stratified data were available. For studies using BW as inclusion criteria, 1000 g was used as a surrogate for 28 weeks, 1500 g for 32 weeks, and 2000 g for 36 weeks. Trials were included if participating infants intended to be managed on noninvasive respiratory support, and randomly assigned to HHHFNC or any other form of noninvasive respiratory support within 24 hours of birth, after extubation from MV or while weaning from noninvasive respiratory support. At least 1 or more of the relevant review outcomes (see below) should have been reported in the results to consider inclusion.

**Search Strategy**

We developed a search strategy by using keywords and Medical Subject Headings (MeSH) terms, as detailed in the Supplemental Information, from 6 databases: Embase, Health Management Information Consortium (HMIC), Medline, Scopus, OpenSIGLE, and Cochrane Central Register of Controlled Trials (CENTRAL). The databases were searched in May 2014. References in included studies were also screened for inclusion. The search included articles in all languages from all countries.

**Outcomes**

Primary outcomes were failure of therapy to establish efficacy, and death, pulmonary air leaks, and nasal trauma to establish safety. Any definition of failure of therapy was considered, because there were differences in how various researchers defined it in trials. Data on several secondary outcomes were collected, including respiratory outcomes (respiratory complications, mode, and length of respiratory support, bronchopulmonary dysplasia [BPD]), intraventricular hemorrhage (IVH), and other relevant neonatal outcomes (sepsis, necrotizing enterocolitis [NEC], patent ductus arteriosus [PDA], retinopathy of prematurity [ROP], etc).

**Definitions**

BPD was defined as respiratory support and/or supplemental oxygen requirement at 36 weeks’ corrected GA. If a room-oxygen test was undertaken at 36 weeks’ corrected GA before categorizing as BPD, then only infants failing the test were considered to have BPD. Grades of IVH were as classified by Papile et al. Classification of NEC was as by Bell et al and modified by Walsh et al. For the purposes of this review, HHHFNC was defined as heated humidified flows in excess of 2 L/min (low flows are defined as <2 L/min). However, most recent articles have used flow rates from 5 to 8 L/min.

**Data Collection**

Data were collected on characteristics of studies and planned outcomes, using a standardized data collection form (Supplemental Table 5) by at least 2 authors independently, and then cross-checked for accuracy. Attempts
were made to clarify methods and request gestation-stratified data from corresponding authors in articles, where both preterm and term infants were included. These are mentioned in the relevant tables in the Results section.

**Statistical Analysis**

*Measurement of Treatment Effect*

Statistical analysis was conducted by using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, Copenhagen, Denmark). For continuous data, the mean and SD (such as duration of respiratory support) were collected and analyzed by using weighted mean differences (WMDs). For categorical data (such as death or treatment failure), data were extracted for each intervention group and odds ratios (ORs) were calculated, along with 95% confidence intervals (CIs). Significance was set at $P < .05$.

One study revealed outcomes as medians and interquartile ranges. Means and SDs were calculated from this data by using methods published previously. For 1 study, some data were read from published figures. Whenever this data were used for pooled estimates of outcome in the meta-analysis, a sensitivity assessment was undertaken to test for differences in estimates.

**Assessment of Bias in Included Studies**

All studies included in final analysis were assessed for risk of bias by using a domain-based flow-sheet (as used by the Cochrane Collaboration). Specific domains examined included selection bias, performance bias, detection bias, attrition bias (low risk: adequate if <10% missing data; high risk: inadequate if >10% missing data), reporting bias, and any other form of bias specific to the design of the study. For each domain, risk of bias was categorized as low risk, high risk, or unknown/unclear risk (if inadequate details were reported in the methods). For each domain, a judgment was made on likely magnitude and direction of the bias, and its likely impact on the outcomes. Disagreements were resolved by consensus. A judgment was made on the overall risk of bias on the basis of the above domains.

**RESULTS**

*Selection of Studies*

Search results and filtering at different stages is represented in Fig 1. Full details of search terms, with the search sequence, is presented in the Supplemental Information section.

*Description of Studies*

Eighteen studies published as full-text articles and 8 studies published as abstracts were initially considered for the review. Of the studies published as full-text articles, 2 used nonheated high-flow therapy, 7 were randomized-sequence cross-over studies, 2 compared different modes of high-flow therapy, and 1 expressed data for nasal trauma as scores. Of the studies published as abstracts, 2 were randomized-sequence cross-over trials and 1 expressed data for nasal trauma as scores. 2 had no raw data suitable for pooling.

![Flow diagram describing stages of search results and filtering process](image-url)

**FIGURE 1** Flow diagram describing stages of search results and filtering process, as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
with MV,\textsuperscript{46} and 1 study included term and preterm infants, without separate data for preterm infants.\textsuperscript{43} These 17 studies were excluded because we were unable to extract relevant data for our analysis (Supplemental Table 8). Thus, 7 studies published as full-text articles and 2 studies published as abstracts were included in the final review (Table 1).

All included studies compared HHHFNC with nCPAP, except 1\textsuperscript{40} that compared infants on HHHFNC with those on NIPPV. All of the studies involved preterm infants who were <37 weeks’ gestation, but 2 studies only included infants born at <32 weeks’ gestation.\textsuperscript{21,27} One study included both term and preterm infants, but stratified data for the preterm infants were supplied by the authors.\textsuperscript{38}

Two studies compared HHHFNC with nCPAP both as a primary mode of respiratory support and as support after extubation from MV.\textsuperscript{33,38} Stratified data for preterm infants supported on HHHFNC as primary mode or after extubation were available from the authors for only 1 of the studies.\textsuperscript{30} Thus, the final analysis included 6 studies where HHHFNC was compared with other forms of NIV as a primary mode of respiratory support\textsuperscript{29,33,38,40,44,45} and 3 studies where these 2 modalities were compared after extubation from MV.\textsuperscript{21,27,33} One study compared the 2 modes while weaning from respiratory support.\textsuperscript{24} One study was only published as an abstract in English, but as full-text article in Persian.\textsuperscript{29} Google Translate was used for an automated translation from Persian to English (Google Inc, Mountain View, CA). Characteristics and clinical details of all included studies are presented in Table 1.

**Risk of Bias in Included Studies**

Eight of the studies were randomized controlled trials, whereas 1 was a quasi-randomized trial.\textsuperscript{33} There was variability of the risk of bias in the included studies (Fig 2), with 6 studies with an overall low risk of bias,\textsuperscript{21,24,27,38,40,45} 2 studies with a high risk of bias because of unclear published methods,\textsuperscript{29,33} and 1 had inadequate information in the abstract to make an informed judgment.\textsuperscript{44}

**Efficacy of HHHFNC**

Efficacy of HHHFNC, compared with other forms of NIV, was assessed primarily by analyzing failure of therapy. Because HHHFNC has been used both as a primary mode of respiratory support as well as after extubation from MV in preterm infants, we conducted separate analyses to compare failure rates. Four studies, involving 321 preterm infants,\textsuperscript{38,40,44,45} compared efficacy of HHHFNC with other NIV when used as a primary mode of respiratory support. Pooled estimates of OR for failure of therapy for these studies was 1.02 (95% CI: 0.55 to 1.88; Fig 3A), and 1.12 (0.51 to 2.50) when the study comparing HHHFNC and NIPPV\textsuperscript{40} was excluded. One of the trials in the primary use group had an uncertain risk of bias\textsuperscript{44}; excluding this from the analysis gave a pooled estimate of failure of 0.85 (0.43 to 1.69). Three trials involving 661 preterm infants\textsuperscript{21,27,38} compared failure rates of HHHFNC with that of other NIV (all used nCPAP) when used as respiratory support after extubation. The pooled OR was 1.09 (0.58 to 2.02; Fig 3B), although there was moderate heterogeneity in the included trials (I\textsuperscript{2} = 56%).

When all 8 eligible trials revealing failure of therapy (any definition) were included, involving 1112 preterm infants, the pooled OR of failure of therapy for HHHFNC versus any other NIV was 1.10 (0.82 to 1.49; Fig 4A). Restricting this analysis to include the 6 studies with overall low risk of bias involving 950 preterm infants, the pooled OR was 1.09 (0.79 to 1.49; Fig 4B). To compare efficacy of HHHFNC versus nCPAP, the trial comparing HHHFNC with NIPPV\textsuperscript{40} was excluded from the analysis. However, this did not significantly change the OR (OR for all studies 1.13 [95% CI: 0.82 to 1.55]; OR for studies with low risk of bias 1.12 [95% CI: 0.80 to 1.56]).

As planned in our protocol, we conducted analyses on gestational subgroups for failure rates of HHHFNC. All of the included studies in our review included infants born at <32 weeks’ GA. However, stratified data on infants born at <32 weeks’ GA was available from only 3 studies.\textsuperscript{21,27,38} Two studies compared efficacy of HHHFNC with nCPAP after extubation from MV\textsuperscript{21,27} whereas the third study used HHHFNC as primary support as well as after extubation from MV.\textsuperscript{38} Pooling all data from these 3 studies, which involved 585 infants, gave an estimated OR of failure of HHHFNC 0.89 (0.42 to 1.89). Including only the 2 studies that compared HHHFNC with nCPAP after extubation (435 infants) gave an estimated OR of failure of HHHFNC, in infants born <32 weeks’ GA, as 1.12 (0.74 to 1.69). Four studies included infants born at <28 weeks’ GA,\textsuperscript{21,27,40,45} whereas 2 more possibly included infants <28 weeks’ GA as derived from their results table.\textsuperscript{33,38} Stratified data were available from 1 of the above studies,\textsuperscript{27} comparing HHHFNC with nCPAP after extubation from MV, giving an OR of 0.54 (0.19 to 1.53, total 59 infants). No stratified data were available from any of the other studies on infants born at <28 weeks’ GA.

To assess time to failure of therapy, we compared failure rates at 3 and at 7 days after study entry. Two studies, involving 443 infants,\textsuperscript{38,44} reported failure of therapy of HHHFNC versus NIV (both nCPAP) ≥72 hours, with a pooled OR of 1.24 (0.66 to 2.32; Supplemental Fig 8A). Four studies, involving a total of 814 infants,\textsuperscript{21,27,38,45} reported failure of therapy of HHHFNC versus NIV (all nCPAP) by 7 days after study entry, with an estimated pooled OR of 1.06 (0.75 to 1.50; Supplemental Fig 8B). In summary, although failure rates were slightly lower in the other NIV
<table>
<thead>
<tr>
<th>Investigators (Study Identifier)</th>
<th>Study Design</th>
<th>Population</th>
<th>When Randomized</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed studies published as full-text</td>
<td>RCT, HHHFNC (2 L/min) versus nCPAP (5 cm H₂O)</td>
<td>Preterm ≥28 wk GA, 80 infants</td>
<td>Weaning from nCPAP</td>
<td>Primary: Duration of oxygen therapy in days Secondary: Duration of respiratory support, nCPAP, hospitalization, weaning, weaning success, need for intubation, complications</td>
<td>&quot;HF&quot; restricted to 2 L/min Objective failure criteria</td>
</tr>
<tr>
<td>Abdel-Hady et al 2011²⁴</td>
<td>RCT, HHHFNC (8 L/min) versus nCPAP (8 cm H₂O)</td>
<td>Preterm &lt;32 wk GA, 132 infants</td>
<td>Postextubation</td>
<td>Primary: Exubation failure up to 7 d Secondary: Nasal trauma, duration of respiratory support and supplemental O₂, BPD (36 wk), IVH, NEC, time to full feeds</td>
<td>Objective failure criteria Boy &gt; girl in nCPAP Data stratified by GA</td>
</tr>
<tr>
<td>Collins et al 2013²⁷</td>
<td>RCT, HHHFNC versus nCPAP</td>
<td>Preterm infants 30–35 wk GA, 70 infants</td>
<td>Within 24 h of birth</td>
<td>Death, NEC, PDA, IVH, CLD, pneumothorax, pulmonary hemorrhage, apnea, sepsis, duration of hospitalization, duration of full enteral feeding, and duration of O₂ need</td>
<td>No raw data in abstract. Used translation.</td>
</tr>
<tr>
<td>Iranpour et al 2011²⁹</td>
<td>RCT, HHHFNC (1–5 L/min) versus NIPPV (ventilator generated)</td>
<td>Preterm infants &lt;35 wk GA and &gt;1000 g BW, 76 infants</td>
<td>Primary support after birth</td>
<td>Primary: Treatment failure (intubation or other mode of NIV) Secondary: clinical features during treatment, respiratory status before MV if needed, &quot;time to stop nasal support,&quot; NM, BPD, nasal trauma, air leaks, GI perforation</td>
<td>Objective failure criteria</td>
</tr>
<tr>
<td>Kugelman et al 2015⁴⁰</td>
<td>RCT, HHHFNC (5–8 L/min) versus bubble nCPAP (5–8 cm H₂O)</td>
<td>Preterm infants &lt;32 wk GA, 303 infants</td>
<td>On first extubation (&lt;36 wk)</td>
<td>Primary: Treatment failure in 7 d Secondary: reintubation during the primary-outcome period, death before hospital discharge, BPD (36 wk), pneumothorax after trial entry, total days of any respiratory support after trial entry, duration of oxygen supplementation after trial entry, length of hospital admission, nasal trauma, sepsis, NEC, ROP, IVH, and PVL.</td>
<td>Designed as noninferiority trial Objective failure criteria HHHFNC &quot;rescued&quot; by nCPAP ITT analysis NIPPV allowed for nCPAP group</td>
</tr>
<tr>
<td>Manley et al 2013²¹</td>
<td>Quasi-randomized prospective controlled trial, HHHFNC versus nCPAP</td>
<td>Preterm infants &lt;37 wk GA, 70 infants</td>
<td>Primary therapy for RDS and at extubation</td>
<td>Death, failure of therapy, intubation and ventilation, days on MV/nCPAP/High-flow, cause of failure, duration of hospital stay, and complications.</td>
<td>Subjective failure criteria</td>
</tr>
<tr>
<td>Phadtare et al 2009⁵⁵</td>
<td>RCT, HHHFNC versus nCPAP</td>
<td>Neonates ≥1000 g BW and ≥28 wk GA 432 infants</td>
<td>At birth and postextubation within 96 h age</td>
<td>Primary: Failure of support within 3 d Secondary: Death, ventilation days, oxygen days, need for delayed intubation, systemic adverse events, local nasal trauma, infant comfort, BPD, time to full feeds</td>
<td>Included term infants Stratified results not published Objective failure criteria</td>
</tr>
<tr>
<td>Yoder et al 2013⁵⁶</td>
<td>RCT, HHHFNC versus nCPAP</td>
<td>Preterm infants 29 –36⁷⁶, 92 infants</td>
<td>At birth on diagnosis of RDS</td>
<td>Primary: intubation within 3 d Secondary: need of surfactant, total duration of respiratory assistance and NIV, length of hospitalization</td>
<td>Failure criteria not specified</td>
</tr>
<tr>
<td>Studies published as abstracts only</td>
<td>RCT, HHHFNC (4–6 L/min) versus nCPAP (4–6 cm H₂O)</td>
<td>Preterm infants 29 –36⁷⁶, 92 infants</td>
<td>At birth on diagnosis of RDS</td>
<td>Primary: intubation within 3 d Secondary: need of surfactant, total duration of respiratory assistance and NIV, length of hospitalization</td>
<td>Failure criteria not specified</td>
</tr>
<tr>
<td>Lavizzari et al 2013⁴⁴</td>
<td>RCT, HHHFNC versus nCPAP</td>
<td>Preterm infants 27–34 wk GA, 28 infants</td>
<td>nCPAP at 6 h of age</td>
<td>Primary: Respiratory failure within 7 d</td>
<td>Objective failure criteria</td>
</tr>
</tbody>
</table>

CLD, chronic lung disease; GI, gastrointestinal; ITT, intention to treat; PVL, periventricular leukomalacia; RCT, randomized controlled trial.
group compared with HHHFNC, it was not statistically significant, regardless of the timing of use of HHHFNC (primary support or after extubation) or the timing of assessment for failure of therapy (3 days or 7 days).

**Safety of HHHFNC**

Safety was assessed by comparing rates of deaths and pulmonary air leaks in the infants supported on HHHFNC and on other modes of NIV. There was no statistically significant difference in the rate of deaths in the group of preterm infants randomly assigned to receive HHHFNC compared with other NIV in the 5 studies revealing this outcome involving 922 infants (OR: 0.48 [0.18 to 1.24]; Fig 5).21,24,27,33,38,40 Similarly, no statistically significant difference between the groups was found in the incidence of any pulmonary air leaks, as reported by 6 trials involving 992 preterm infants,21,24,27,33,38,40 with an OR of 0.72 (0.28 to 1.83; Fig 6).

**Nasal Trauma**

Injury of the nasal mucosa or external nares is often reported on preterm infants who are supported on nCPAP.49,50 Five studies involving 857 infants21,29,33,38,40 revealed the incidence of nasal trauma in infants supported on HHHFNC compared with other forms of NIV. One more trial26 revealed nasal trauma, but as scores rather than events, and could not be included in the analysis. Pooled OR for incidence of nasal trauma in preterm infants receiving HHHFNC was 0.13, which was significantly lower (P = .02) than infants supported on other forms of NIV (95% CI: 0.02 to 0.69; Fig 7), although significant heterogeneity was detected between the trials. Excluding the 2 trials with a high risk of bias, OR for nasal trauma was still significantly lower in infants (total 717) supported on HHHFNC (0.33; 0.13 to 0.87, P = .02).

**Secondary Outcomes**

Other relevant outcomes of preterm infants were compared between the groups, as planned in our analysis (Table 2). Odds of all secondary outcomes analyzed were comparable in the 2 groups of infants.

**DISCUSSION**

From our analysis, supporting preterm infants on HHHFNC was equivalent in efficacy as any other form of NIV (NIPPV or nCPAP). This efficacy was mainly observed in the moderate to late preterm infants ($\geq 28$ weeks’ gestation at birth), and after extubation from MV. HHHFNC had similar failure rates to the other modes when used both as a primary mode of respiratory support after birth, as well as support after extubation from MV, although the number of infants who were supported on HHHFNC at birth was limited. Efficacy was maintained over time, as assessed by failure of therapy at 3 days and at 7 days after trial entry. There were no statistically significant differences in the odds of death or air leaks in infants supported on HHHFNC compared...
with other modes of NIV. However, significantly fewer infants had nasal trauma as a complication when supported on HHHFNC compared with other forms of NIV.

We have assessed efficacy by comparing rates of failure of therapy of a particular mode of support. "Failure of therapy" was variably defined by different studies. Six of the studies included in our analysis had published objective criteria in the methods to define failure of therapy, which included a combination of clinical (observation

**FIGURE 3**

Pooled estimates of odds of failure of therapy of HHHFNC compared with other modes of NIV in preterm infants, when used as (A) primary mode of respiratory support, and (B) after extubation from MV.

<table>
<thead>
<tr>
<th>Study Subgroup</th>
<th>High Flow Events</th>
<th>NIV Events</th>
<th>Total Events</th>
<th>Weight % M-H, Fixed 95% Cl</th>
<th>OR M-H, Fixed 95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kugelman et al 2019</td>
<td>12</td>
<td>38</td>
<td>13</td>
<td>38</td>
<td>44.0 0.89 (0.34 to 2.31)</td>
</tr>
<tr>
<td>Lavizzari et al 2013</td>
<td>5</td>
<td>40</td>
<td>3</td>
<td>52</td>
<td>11.3 2.33 (0.52 to 10.41)</td>
</tr>
<tr>
<td>Nair and Kama 2006</td>
<td>2</td>
<td>13</td>
<td>2</td>
<td>15</td>
<td>7.8 1.18 (0.14 to 9.83)</td>
</tr>
<tr>
<td>Yoder et al 2013</td>
<td>6</td>
<td>58</td>
<td>9</td>
<td>67</td>
<td>37.0 0.74 (0.25 to 2.23)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>149</td>
<td>172</td>
<td>100.0</td>
<td>1.02 (0.55 to 1.88)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>25</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity; $\chi^2 = 1.56$, df = 3 (P = .66); $\text{I}^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect; Z = .06 (P = .95)</td>
<td></td>
<td></td>
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</tbody>
</table>

**FIGURE 4**

Pooled estimate of odds of failure of therapy in preterm infants supported on HHHFNC compared with other modes of NIV (A) including all eligible studies, and (B) studies with a low risk of bias only.

<table>
<thead>
<tr>
<th>Study Subgroup</th>
<th>High Flow Events</th>
<th>NIV Events</th>
<th>Total Events</th>
<th>Weight % M-H, Random 95% Cl</th>
<th>OR M-H, Random 95% Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collins et al 2013</td>
<td>15</td>
<td>67</td>
<td>22</td>
<td>65</td>
<td>31.0 0.56 (0.26 to 1.22)</td>
</tr>
<tr>
<td>Marley et al 2013</td>
<td>52</td>
<td>152</td>
<td>39</td>
<td>151</td>
<td>43.2 1.49 (0.91 to 2.45)</td>
</tr>
<tr>
<td>Yoder et al 2013</td>
<td>11</td>
<td>107</td>
<td>9</td>
<td>119</td>
<td>25.7 1.40 (0.56 to 3.52)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>326</td>
<td>335</td>
<td>100.0</td>
<td>1.09 (0.58 to 2.02)</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>78</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity; $\chi^2 = 0.17$, $\chi^2 = 4.53$, df = 2 (P = .10); $\text{I}^2 = 56%$</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Test for overall effect; Z = .26 (P = .80)</td>
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<td></td>
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</table>

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of vitals, respiratory effort, apneas, oxygen requirement) and biochemical (blood gas characteristics) criteria. Although there were minor differences in the thresholds, the criteria published by these trials were largely similar (Supplemental Table 9). The 3 other studies did not publish objective criteria in their methods to define failure of therapy. All 3 of these studies were deemed to have a high risk of performance and detection bias. However, on separate analysis, both including and excluding the studies with a high risk of bias, the pooled OR for failure of therapy remained very similar (results section "efficacy of therapy"). Nevertheless, it is important that future studies attempt to define "failure" more accurately and uniformly, for results to be easily comparable between different studies.

Studies with a low risk of bias (Fig 4B) defined failure of therapy by objective criteria. However, not all failures necessarily resulted in reintubation for MV, suggesting that "failure of 1 mode of NIV" is not the same as "failure of NIV." In our opinion, this is an important distinction to make, as overall the neonatal community seems to be moving toward increased use of NIV, which has shown clinical benefit. A time-based definition of failure has its own disadvantages, as some infants continue to "fail" even after the defined study period, especially the extreme preterm group.

A common complication among preterm infants supported on nCPAP is nasal injury, which can vary from 20% to 60%. The higher rates were observed in the smaller and extreme preterm infants. Our analysis suggests significantly lower odds of nasal trauma (defined and measured variably) in preterm infants supported on HHHFNC, compared with other modes of nCPAP. In addition, preterm infants are thought to be more comfortable on HHHFNC by neonatal nurses compared with nCPAP, although no difference in patient comfort was detected while on HHHFNC as compared with nCPAP in a recent trial.

HHHFNC is the most recent mode of NIV in adults and neonatal patients. However, the precise mechanism of action, resulting in clinical benefit, has not been fully evaluated. Proposed theories include washout of anatomic dead space in the upper airways because of the flow of gas, improvement in conductance of gas because of humidification, reduction in metabolic demands of the airways from the warm and humidified gas, and provision of distending pressure to the lungs. Extrathoracic anatomic dead space is related to age and is higher in small infants (>3 mL/kg) compared with adults. Thus, continuous washout of this relatively large space with a supply of fresh gas could be of clinical benefit, especially in the neonatal period. In contrast to nCPAP (or BiPAP), which depend on a seal to provide distending pressure, a seal at the upper airways is not required for HHHFNC. Thus, the distending pressure provided by HHHFNC is dynamic, depending on the phase of the respiratory cycle. All of these...
mechanisms, in theory, suggest HHHFNC could be suited to the anatomy and physiology of preterm infants. Additionally, HHHFNC seems to cause less nasal trauma in preterm infants, and seems to be preferred by nurses and parents. However, because of the physiology of the lungs in early respiratory distress syndrome (RDS), the continuous distending pressure provided by nCPAP, in theory, could make it more suitable as a mode of respiratory support than HHHFNC.

HHHFNC systems have been in use in both adults and infants since the early 2000s. To our knowledge, this is the first detailed systematic review comparing HHHFNC with other modes of NIV in preterm infants, with a view to pooling all of the data together and providing evidence for this popular mode of respiratory support than HHHFNC.

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TABLE 2 Summary of Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total Number of Infants</th>
<th>Study Reference</th>
<th>Pooled Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total duration of respiratory support</td>
<td>818</td>
<td>21,24,38,40,45</td>
<td>1.28</td>
<td>-0.91 to 3.48</td>
</tr>
<tr>
<td>Length of stay on neonatal unit</td>
<td>860</td>
<td>21,24,33,38,40</td>
<td>0.81</td>
<td>2.38 to 4.01</td>
</tr>
<tr>
<td>BPD</td>
<td>932</td>
<td>21,27,33,38,40</td>
<td>0.83</td>
<td>0.67 to 1.28</td>
</tr>
<tr>
<td>PDA, any</td>
<td>870</td>
<td>21,29,33,38,40</td>
<td>0.97</td>
<td>0.66 to 1.42</td>
</tr>
<tr>
<td>PDA requiring treatment</td>
<td>654</td>
<td>21,38</td>
<td>0.84</td>
<td>0.55 to 1.30</td>
</tr>
<tr>
<td>IVH, any</td>
<td>711</td>
<td>21,27,29,33,38,40</td>
<td>0.63</td>
<td>0.51 to 1.18</td>
</tr>
<tr>
<td>IVH, grade III/IV</td>
<td>495</td>
<td>21,24,27</td>
<td>0.48</td>
<td>0.19 to 1.21</td>
</tr>
<tr>
<td>ROP, any</td>
<td>720</td>
<td>21,38</td>
<td>0.97</td>
<td>0.38 to 2.46</td>
</tr>
<tr>
<td>Sepsis</td>
<td>880</td>
<td>21,24,39,40,45</td>
<td>1.07</td>
<td>0.69 to 1.75</td>
</tr>
</tbody>
</table>

a All infants in included studies.  
b High-flow versus NIV.  
c Weighted mean difference in days.  
d OR.
should be based on data from studies with a low risk of bias.

Results of our analysis suggest that HHHFNC is not inferior to other modes of NIV in preterm infants. Due to significantly lower odds of nasal trauma, and no significant differences in other common neonatal outcomes, HHHFNC may be a preferred method in this GA group. Caution needs to be exercised in the more preterm infants, where efficacy and safety of HHHFNC, either as a primary mode of support or after extubation, are not yet thoroughly tested.

Future research needs to concentrate on the extreme preterm group of infants, who would benefit most from modes of NIV. Weaning of NIV is another area of practice that needs further research, as a recent review on weaning of HHHFNC in preterm infants was unable to identify any eligible studies on this subject.58 We feel that our data provide evidence to consider HHHFNC as a mode of respiratory support in preterm infants by clinicians.

REFERENCES


ABBREVIATIONS

BiPAP: bilevel nasal continuous positive airway pressure
BPD: bronchopulmonary dysplasia
BW: birth weight
CI: confidence interval
GA: gestational age
HHHFNC: heated humidified high-ﬂow nasal cannula
IVH: intraventricular hemorrhage
MeSH: Medical Subject Headings
MV: mechanical ventilation
nCPAP: nasal continuous positive airway pressure
NEC: necrotizing enterocolitis
NIPPV: noninvasive positive pressure ventilation
NIV: noninvasive ventilation
OR: odds ratio
PDA: patent ductus arteriosus
RDS: respiratory distress syndrome
ROP: retinopathy of prematurity

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MEASURING SCREAMS: I was recently at a play I had seen before. I knew that it was suspenseful and that soon a scream would be heard. I was somewhat prepared but, nonetheless, the sudden piercing scream made me flinch. Around me, many in the audience practically jumped from their seats and programs were sent flying. The scene made me wonder why we all were so startled by the noise.

According to The New York Times (Science: July 16, 2015), researchers have determined what makes us react to screams. Surprisingly, at least to me, it isn’t necessarily the loudness, pitch, or shrillness that makes us react. Scientists analyzing screams in movies and those recorded in a laboratory found that during a scream, the loudness of the sound changes. During normal conversation, the loudness of speech ranges between 4 and 5 hertz. In a scream, the loudness can range from 30 to 150 hertz. Roughness, which describes how fast the loudness of a sound changes, is a critical component of what makes a scream alarming - or scary. The greater the roughness of the scream, the more alarming it is. Researchers have studied the effects of screams on brain function using functional magnetic resonance imaging. Screams trigger activity in the amygdala, an area of the brain that registers and remembers fears. The greater the roughness of the scream, the greater the activity triggered in the amygdala. Sounds in the environment associated with a lot of roughness turn out to be those used in emergency vehicles such as ambulances. While ambulance sirens were not necessarily designed with roughness in mind, they are, like the scream in the play I was watching, quite attention getting - which, in the case of getting out of the way of an oncoming ambulance, is a good thing to do.

Noted by WVR, MD