Comparison Between Continuous Positive Airway Pressure and High-Flow Nasal Cannula as Postextubation Respiratory Support in Neonates: A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: The interest in noninvasive respiratory support has been increasing, including continuous positive airway pressure and recent respiratory methods, namely high-flow nasal cannula. It is discussed if high-flow nasal cannula can reduce continuous positive airway pressure or invasive ventilation use. This systematic review and meta-analysis aimed to compare continuous positive airway pressure and high-flow nasal cannula as postextubation respiratory support in neonates.

Materials and Methods: A literature search, based on Preferred Reporting of Items of Systematic Reviews and Meta-Analyses guidelines, was conducted across MEDLINE (through PubMed), Scopus, and Web of Science in 15 years (2006-2021) assessing randomized controlled trials that compared continuous positive airway pressure with high-flow nasal cannula as postextubation interventions in neonates. The primary outcome was extubation failure at 72 hours and/or at 7 days and the secondary outcomes included air leak syndrome, pneumothorax, bronchopulmonary dysplasia, nasal trauma, abdominal distension, and mortality.

Results: Seven studies were included, comprising 1044 neonates. No statistically significant differences were found between high-flow nasal cannula and continuous positive airway pressure in extubation failure (at 72 hours and/or at 7 days), air leak syndrome, pneumothorax, bronchopulmonary dysplasia, abdominal distension, and mortality. High-flow nasal cannula was associated with a lower incidence of nasal trauma (odds ratio = 0.21; 95% CI 0.08-0.52; P = .0008). Studies assessing extreme premature infants (<28 weeks) raised some efficacy and safety concerns.

Conclusion: High-flow nasal cannula may be as effective and safe as continuous positive airway pressure, with similar extubation failure and risk of air leak syndrome, pneumothorax, bronchopulmonary dysplasia, abdominal distension, and mortality with the advantage of less nasal trauma. High-flow nasal cannula should be considered as an alternative to continuous positive airway pressure in postextubation settings in neonates. Further studies are needed to establish efficacy and safety in lower gestational ages.

Keywords: Continuous positive airway pressure, high-flow nasal cannula, infant, newborn

INTRODUCTION

Respiratory support is frequently used in neonatology, mainly in premature infants. Respiratory problems remain one of the most common causes of morbidity in this population, and invasive respiratory support is frequently required, despite its associated risks.

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The interest and use of noninvasive respiratory support have long been increasing, including continuous positive airway pressure (CPAP), and more recently high-flow nasal cannula (HFNC).1,2 Invasive ventilation is still associated with various prematurity morbidities, such as bronchopulmonary dysplasia (BPD).3,4 To prevent lung injury and respiratory complications, noninvasive ventilation has gained importance over time in neonatology. However, invasive ventilation remains the first and only option in certain situations and therefore cannot always be avoided. Reducing the duration of its exposure and promptly extubating these infants as soon as possible can greatly impact their short- and long-term morbidity.4

One of the most used noninvasive respiratory support modes worldwide is CPAP which delivers a distending pressure continuously to the lungs between 5 and 10 cm of water, using humidified and heated gases.5 Continuous positive airway pressure can be used both in primary respiratory support and after extubation from invasive ventilation, and it is thought to reduce intrapulmonary shunt and improve functional residual capacity by preventing alveolar collapse at end-expiration, promoting its recruitment, and stabilizing the chest wall.6,7 It is also thought to reduce the work of breathing. Although CPAP has many obvious advantages, it also presents some risks, such as the development of air leak syndromes, mainly pneumothorax, gastric insufflation, and hyperinflation of the lungs, which can reduce compliance and increase the work of breathing and damage to the nasal septal mucosa with possible necrosis due to the fixing devices and nasal irritation.7 Moreover, CPAP can affect sucking patterns and feeding, positioning, and parental bonding.5

High-flow nasal cannula is an alternative noninvasive respiratory device that uses heated humidified oxygen given through small prongs at a flow above 1 L/min.6,8 It is also used either for primary respiratory support or after extubation from invasive ventilation and has recently gained importance in neonatology.10,11 Lately, it has been discussed if HFNC can reduce the use of CPAP and invasive ventilation, which are more-invasive and less-tolerated respiratory devices.2 Compared to these, HFNC is easier to apply and presents greater access to the infant’s face, allowing an improvement in feeding and parental bonding.12 In addition, HFNC may reduce the work of breathing, eliminate the dead space, improve lung compliance at higher flow rates, and reduce nasal injury. Nevertheless, it can be associated with risk of infection, mucosal irritation, nasal obstruction, or bleeding, along with the unpredictability of the positive airway pressures generated.5,13

The aim of this systematic review and meta-analysis, was to analyze the current literature assessing and comparing the use of CPAP and HFNC as postextubation respiratory support in neonates. This review shall provide insights into current knowledge of HFNC’s efficacy and safety and provide suggestions for future practice. The primary outcome was extubation failure at 72 hours and/or 7 days, and the secondary outcomes included BPD, air leak syndrome, nasal trauma, pneumothorax, abdominal distension, and mortality.

**MATERIALS AND METHODS**

**Design**

A review was conducted based on the Preferred Reporting of Items of Systematic Reviews and Meta-Analyses (PRISMA).13

**Eligibility Criteria**

This review included randomized controlled trials published from October 2006 to September 2021 that compared CPAP and HFNC as postextubation respiratory support in neonates. Articles were excluded if they presented a crossover design, evaluated the use of HFNC and CPAP as a primary intervention, included other interventions than HFNC or CPAP, would not analyze exclusively neonates, or did not include the main outcome, that is, extubation failure at 72 hours and/or 7 days. Duplicate articles, comments, literature or systematic reviews, editorial letters, and those not related to the purpose of this review were also excluded. The search strategy was restricted to human studies, and no language restrictions were applied.

**Data Sources and Search Strategy**

Through October 6, 2021, an extensive literature search was conducted in 3 electronic databases: MEDLINE (through PubMed), Scopus, and Web of Science. The search query for this study was the following: ("CPAP Ventilation" OR "Ventilation, CPAP" OR “Nasal Continuous Positive Airway Pressure” OR “nCPAP Ventilation” OR “Ventilation, nCPAP” OR “Airway Pressure Release Ventilation” OR “APRV Ventilation Mode” OR “APRV Ventilation Modes” OR “Ventilation Mode, APRV” OR “Ventilation Modes, APRV” OR “Biphasic Continuous Positive Airway Pressure” OR “BiPAP Biphasic Positive Airway Pressure” OR “BiPAP Biphasic Positive Airway Pressure” OR “BiPAP Bilevel Positive Airway Pressure” OR “Biphasic Positive Airway Pressure” OR “Bilevel Continuous Positive Airway Pressure” OR “Bilevel Positive Airway Pressure”) AND ("Infants, Newborn" OR “Newborn Infant” OR “Newborn Infants” OR “Newborns” OR “Newborn” OR “Neonate” OR “Neonates”) AND ("High-Flow Nasal Cannula” OR “Heated Humidified High-Flow Nasal Cannula” OR “HFNC” OR “HHHFNC” OR "HFT" OR "Vapotherm” OR “Nasal High-Flow” OR “Heated Humidity High-Flow Nasal Cannula” OR “High-Flow”.)

**Study Selection**

The first analysis included a screening of all article titles and abstracts to identify relevant studies. References were cross-checked to retrieve articles missed on the initial search. The second analysis included a full-text screening of the selected articles. Eligibility assessment was independently done by 2 reviewers (C.M. and R.P.) in a blinded, standardized manner. Disagreements between the reviewers were resolved by discussion and consensus.

**Data Collection Process and Outcomes**

Data extraction involved 2 independent reviewers (C.M. and R.P.) using a standardized data extraction sheet followed by cross-checking and discussion of results. Information was extracted from each included trial on study characteristics (total number of participants, number of participants allocated to CPAP and HFNC, study duration, gestational age, birth weight, and pathology) and evaluated outcomes.

**Outcomes**

The primary outcome of this systematic review was extubation failure at 72 hours and/or 7 days. The secondary outcomes...
included BPD, air leak syndrome, nasal trauma, pneumothorax, abdominal distension, and mortality.

**Risk of Bias Assessment**
The risk of bias in the included studies was assessed by 2 reviewers (C.M. and R.P.) independently using the National Institutes of Health Quality Assessment of Controlled Intervention Studies. The rankings assigned to the included studies were “yes,” “no,” or “not reported,” and the risk of bias was categorized as “good,” “fair,” or “poor.”

**Statistical Analysis and Synthesis of Results**
Meta-analysis was carried out in the RevMan® 5.4 software. Eight outcomes were selected to be included in the meta-analysis: extubation failure at 72 hours and 7 days, BPD, air leak syndrome, pneumothorax, abdominal distension, nasal trauma, and mortality. The retrieved data from the included studies were used to calculate odds ratio (OR) with 95% CIs for dichotomous parameters. The Cochrane Q and I² statistic were used to calculate heterogeneity, where values of I² between 25% and 50% were categorized as low heterogeneity, values between 50% and 75% were classified as moderate heterogeneity, and values superior to 75% were classified as substantial heterogeneity. A value of P < .05 was considered statistically significant. A random-effects analysis was implemented, to obtain more conservative results.

**RESULTS**

**Study Selection**
Through database search, 491 articles were identified, 254 in MEDLINE, 159 in Scopus, and 78 in Web of Science. After duplicate elimination, there were 300 articles for analysis. The abstract and title of these records were screened, and 21 records were included for full-text analysis. In this second phase, 14 articles were excluded based on the previously defined exclusion criteria: 4 did not include the primary end point, 4 did not analyze CPAP and HFNC individually, 3 had a different study design, and 3 did not focus on postextubation (1 post-INSURE intervention, 1 primary intervention, and 1 with primary and postextubation intervention together). In the end, 7 studies were included in this systematic review, with a total of 10,44 newborns. A detailed study flow diagram is presented in Figure 1.

**Study Characteristics**
Characteristics of included studies are summarized in Table 1. Selected studies have representation in 3 different continents and 5 countries, including 2 from Australia, 2 from China, 1 from Egypt, 1 from Thailand, and 1 from India. Study duration ranged from a minimum of 14 months and a maximum of 35 months and included data from 2009 to 2018. Most studies were single centered, with only 1 study being multicentered. The gestational age of the neonates included ranged from 26 to 42 weeks and the mean birth weight ranged from 600 to 3893 g. Six studies included only premature infants and 1 study included only term newborns. One study included only neonates with specific conditions, namely meconium aspiration syndrome and persistent pulmonary hypertension of the newborn.

**Risk of Bias Assessment**
All eligible studies were rated as “good” after the risk of bias assessment, as detailed in Table 2.

**Results of Individual Studies**
The main results of individual studies are summarized in Table 3.

**Extubation Failure.** Extubation failure definition was similar across studies, including the presence of apnea, increasing breathing effort or fraction of inspired oxygen (FiO2) need, and altered blood analysis (acidosis, elevated partial pressure of carbon dioxide, or low partial pressure of oxygen). Definitions of extubation failure are summarized in Table 4. Three studies analyzed extubation failure at 72 hours, and 1 of them reported data for both 72 hours and 7 days. No study found a statistically significant difference in this outcome.

Meta-analysis performed for extubation failure at 72 hours involved a total of 448 patients, and extubation failure at 7 days involved a total of 789 patients. There were no statistically significant differences between HFNC and CPAP groups concerning extubation failure at 72 hours (OR = 1.33; 95% CI 0.67–2.63; P = .41) or at 7 days (OR = 1.18; 95% CI 0.73–1.89; P = .5). Moderate heterogeneity between studies was found in extubation failure at 7 days (I² = 54%). Forest plots of these variables are presented in Figure 2A and B.

Four studies reported analysis of extubation failure in extremely preterm neonates. Considering only preterm neonates born between 26 and 28 weeks, Kang et al. found a statistically significant higher extubation failure rate in the HFNC group compared to those in the CPAP group. However, the reintubation rate demonstrated no statistically significant difference. Collins et al. also reported that extubation failure rates at 7 days were greater in neonates born before 28 weeks, opposing to higher gestational ages. Soonsawad et al. found that all the neonates who required reintubation and 71% of neonates who met the criteria for extubation failure at 72 hours were born before 28 weeks gestation. Accordingly, Manley et al. reported a higher extubation failure rate at 7 days in these neonates, despite the assigned treatment, with a risk difference of 20% favoring CPAP, besides not having enough power to assess the safety or efficacy of HFNC in this group. Considering very premature infants (born before 32 weeks), the same authors found that HFNC was noninferior to CPAP, with a difference of 8.4% favoring CPAP. Furthermore, about half of the neonates were treated with success with CPAP without reintubation when treatment with HFNC failed, which resulted in a nonstatistically significant difference between groups in reintubation within 7 days after extubation.

**Air Leak Syndrome and Pneumothorax.** Three studies evaluated air leak syndrome and 5 studies specifically analyzed pneumothorax incidence. Regarding air leak syndrome, no study found a statistically significant difference in this outcome. Meta-analysis performed for air leak syndrome involved a total of 367 patients. There were no statistically significant differences between HFNC and CPAP concerning this outcome (OR = 0.24; 95% CI 0.03–2.25; P = .21). Low heterogeneity between studies was found (I² = 0%). A forest plot of this variable is shown in Figure 2C.
With respect to pneumothorax incidence, no statistically significant difference was found between HFNC and CPAP groups. Meta-analysis performed for pneumothorax involved a total of 805 patients, with no statistically significant differences between groups (OR = 0.81; 95% CI 0.23–2.86; P = .74). Low heterogeneity between studies was found (I² = 37%). A forest plot of this variable is shown in Figure 2D.
Bronchopulmonary Dysplasia. The definition of BPD was presented in only 3 studies,\[16-21\] which characterized it as the need for supplemental oxygen or respiratory support at 36 weeks.

Five studies analyzed BPD,\[16-21\] and the majority found no statistically significant difference in this outcome. Opposingly, 1 study\[19\] reported a statistically significant higher incidence in the HFNC group, compared to CPAP.

Meta-analysis performed for BPD involved a total of 966 patients, with no statistically significant differences between groups (OR = 1.25; 95% CI 0.59-2.65; \( P = .56 \)), besides substantial heterogeneity between studies (\( I^2 = 70\% \)). A forest plot of this variable is shown in Figure 2F.

Nasal Trauma. Five studies analyzed nasal trauma.\[15,17,19-21\] There was a statistically significant higher incidence of nasal trauma in the HFNC group, compared to the CPAP group.

Meta-analysis performed for nasal trauma involved a total of 663 patients, and no statistically significant differences were found between HFNC and CPAP groups (OR = 1.25; 95% CI 0.59-2.65; \( P = .56 \)), besides substantial heterogeneity between studies (\( I^2 = 70\% \)). A forest plot of this variable is shown in Figure 2E.

Abdominal Distension. Only 2 studies evaluated abdominal distension,\[17,19\] with opposing results. One study found no statistically significant difference between groups,\[19\] as the other reported a statistically significant higher incidence in the HFNC group, compared to CPAP.\[17\]

Meta-analysis performed involved a total of 271 patients, with no statistically significant differences between groups (OR = 0.39; 95% CI 0.08-1.76; \( P = .22 \)), besides substantial heterogeneity between studies (\( I^2 = 77\% \)). A forest plot of this variable is shown in Figure 2G.

Mortality. Six studies reported mortality rates,\[15,16,18-21\] with no statistically significant difference found between groups. Most studies reported rates below 5%, except for 1 study\[19\] which found rates of 9.1% and 10.5% for HFNC and CPAP groups, respectively.

Meta-analysis performed for this outcome involved a total of 966 patients, with no statistically significant differences between HFNC and CPAP groups (OR = 0.83; 95% CI 0.45-1.53; \( P = .55 \)). Low heterogeneity between studies was found (\( I^2 = 0\% \)). A forest plot of this variable is presented in Figure 2H.

Other Findings: Intraventricular Hemorrhage, Necrotizing Enterocolitis, Feeding, Respiratory Support, and Hospital Stay Duration. Concerning intraventricular hemorrhage (IVH), 3 studies found no statistically significant differences and Collins et al\[16-18\] specifically found no statistically significant differences in IVH grade 3+ between the CPAP and HFNC groups. Regarding necrotizing enterocolitis (NEC), 2 studies found no statistically significant differences and Collins et al\[16-18\] particularly reported no statistically significant differences in NEC bell stage 2+ between the 2 groups.

Concerning feeding, different results were found with no statistically significant differences. Gao et al\[17\] reported a trend of shorter time to full enteral feeding in the HFNC group, although...
there was not a statistically significant difference. Oppositely, Morsy et al. disclosed that the time to reach full enteral feedings was shorter in patients extubated to CPAP, although this difference was not statistically significant. On the other hand,
Figure 2. Meta-analysis forest plots. (A) Extubation failure at 72 hours; (B) extubation failure at 7 days; (C) air leak syndrome; (D) pneumothorax; (E) bronchopulmonary dysplasia (BPD); (F) nasal trauma; (G) abdominal distension; and (H) mortality.
2 studies found no statistically significant differences concerning the time to reach the full enteral feed.\textsuperscript{16,21} Concerning respiratory support duration, Morsy et al\textsuperscript{19} found that the number of days spent on CPAP was higher than those spent on HFNC, with a statistically significant difference. Gao et al\textsuperscript{17} reported that there was a tendency for a shorter duration of noninvasive ventilatory support in the HFNC group, although there was no statistically significant difference.

Concerning hospital stay duration, Gao et al\textsuperscript{17} found that there was a tendency for a shorter duration of hospitalization in the HFNC, with no statistically significant difference, and Yengkhom et al\textsuperscript{21} reported that there was no statistically significant difference between the 2 groups concerning hospital stay duration.

DISCUSSION

High-flow nasal cannula has increasingly been used in neonatology as an alternative to CPAP. However, there are still questions to be addressed regarding its efficacy, safety, and short- and long-term outcomes.\textsuperscript{16,21} High-flow nasal cannula has potential advantages. The humidified gas in the airway can reduce the metabolic work of the lung and enhance its conductivity and compliance. Additionally, it can reduce the dead space of the nasopharynx, decreasing its expiratory and inspiratory resistance, reducing the inhalation of carbon dioxide in re-inhalation, and generating pressure that can be as effective as CPAPs, through positive air pressure added into the nasopharynx.\textsuperscript{18} Moreover, the HFNC prongs are smaller, shorter, and narrower compared to CPAP, causing potentially less nasal trauma, and the humidified gas could help maintain respiratory mucosal integrity. Damage to the nasal mucosa can lead to septicemia, particularly in preterm neonates. Furthermore, the prongs used in HFNC should not obstruct more than 50% of the nares, opposing to the CPAP prongs, which have to attain a seal with the nares and, consequently, present unavoidable pressure effects.\textsuperscript{22} Other potential advantages of HFNC over CPAP can include easier device application and potential easier feeding, positioning, and parental bonding.\textsuperscript{5} However, in specific conditions, CPAP can be superior to HFNC, such as in neonates with chronic lung disease, because, even though HFNC uses positive end-expiratory

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Table 1

| Study or Subgroup  | HFNC Events | CPAP Events | Odds Ratio | Year |
|-------------------|-------------|-------------|------------|------|
| Manley, BJ et al, 2013 | 60 | 152 | 26.3% | 0.55 [0.35, 0.87] | 2013 |
| Soonsawad S et al, 2017 | 4 | 24 | 17.7% | 0.25 [0.07, 0.97] | 2017 |
| Gao XY et al, 2017 | 2 | 40 | 15.4% | 0.11 [0.02, 0.55] | 2017 |
| Yengkhom R. et al, 2021 | 5 | 88 | 21.3% | 0.07 [0.03, 0.19] | 2021 |
| Morsy, RS et al, 2021 | 5 | 88 | 19.3% | 0.25 [0.08, 0.80] | 2021 |

Total (95% CI): 367 / 384 (100.0%)

Odds Ratio: 0.21 [0.08, 0.52]

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Table 2

| Study or Subgroup  | HFNC Events | CPAP Events | Odds Ratio | Year |
|-------------------|-------------|-------------|------------|------|
| Gao XY et al, 2017 | 3 | 40 | 42.0% | 0.16 [0.04, 0.60] | 2017 |
| Morsy, RS et al, 2021 | 38 | 88 | 58.0% | 0.75 [0.42, 1.32] | 2021 |

Total (95% CI): 128 / 143 (100.0%)

Odds Ratio: 0.39 [0.08, 1.76]

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Table 3

| Study or Subgroup  | HFNC Events | CPAP Events | Odds Ratio | Year |
|-------------------|-------------|-------------|------------|------|
| Manley, BJ et al, 2013 | 5 | 152 | 25.4% | 0.82 [0.25, 2.75] | 2013 |
| Collins CL et al, 2013 | 1 | 67 | 7.1% | 0.31 [0.03, 3.09] | 2013 |
| Kang WQ et al, 2016 | 3 | 79 | 11.3% | 1.58 [0.26, 9.71] | 2016 |
| Soonsawad S et al, 2017 | 0 | 24 | 25 | Not estimable | 2017 |
| Yengkhom R. et al, 2021 | 8 | 88 | 40.5% | 0.85 [0.33, 2.23] | 2021 |

Total (95% CI): 473 / 493 (100.0%)

Odds Ratio: 0.83 [0.45, 1.53]

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Figure 2. Continued
pressure, it is believed that CPAP provides better adequate positive pressure respiratory support than HFNC.25

This systematic review assessed the advantages and disadvantages of HFNC and CPAP by analyzing 7 worldwide randomized controlled trials, which included a total of 1044 neonates.

As regards the primary end point, extubation failure, the main efficacy variable, there were no statistically significant differences between HFNC and CPAP groups, both at 72 hours and at 7 days. Regarding safety issues, there was no statistically significant difference in air leak syndrome, including pneumothorax, BPD, abdominal distension, or mortality. High-flow nasal cannula, however, was associated with a lower incidence of nasal trauma compared to CPAP. Colleti et al, Fleeman et al, and Wilkinson et al reported no statistically significant differences in extubation failure. Colleti et al, Fleeman et al, Hong et al, and Wilkinson et al presented similar results to those disclosed in this systematic review, stating that there were no statistically significant differences in BPD and mortality between the 2 groups. However, and contrasting with this systematic review, Morsy et al reported a statistically significant higher rate of BPD in the HFNC, compared to the CPAP group. Colleti et al found no differences in pneumothorax incidence between the 2 groups. Consequently, HFNC appears to be safe, with the benefit of significantly lower nasal trauma.25 Opposingly to this systematic review, Fleeman et al found a significantly lower incidence of air leak syndrome in the HFNC group, and Wilkinson et al and Hong et al disclosed a significantly lower pneumothorax incidence in the HFNC group.

A study not included in this review analyzed the electrical activity of the diaphragm and found no difference in breathing effort in premature infants with HFNC (6 L/min) compared with CPAP (3 cmH2O), suggesting that HFNC could replace CPAP when the neonate is prepared for weaning.25

Regarding the efficacy of HFNC in the extreme premature groups, the results are not conclusive, and a higher risk of extubation failure appears to exist. Kanbar et al also found that after extubation, and while receiving HFNC, compared to CPAP, this group had higher FiO2 demands and substantially longer respiratory pauses, which raises doubt if this respiratory support method should be used as postextubation in this specific group. Morsy et al equally reported that the use of HFNC in this group was questionable, enhancing that more studies, especially with numerous neonates and multicenter studies, are required to analyze this topic. It is relevant to mention that Manley et al reported the use of rescue CPAP in the HFNC group following treatment failure, which demonstrates that CPAP can be used if treatment with HFNC fails, particularly in this group.

Concerning other potential advantages of HFNC, such as less interference with feeding compared to CPAP, only a few studies addressed this outcome, and the results reported were inconsistent. None of the studies analyzed the easiness of the application of the devices or the advantage of parental bonding. Glackin et al found no benefits of HFNC compared to CPAP in the institution of oral feeds in preterm neonates and Yengkhom et al disclosed no difference in duration of total parenteral nutrition and conversion to time to full enteral feeds, even though abdominal distension is a frequent problem when using CPAP. Opposingly, Charki et al reported that neonates in the HFNC group had fewer days to achieve full feeds. Regarding bonding, Engesland et al reported, from a nurses’ perspective, that HFNC can be better for neonates, because it promotes bonding between newborns and parents, improving their relationship, mostly due to greater access to the baby’s face. Also, it was reported that parents considered HFNC a less intensive, quieter, and simpler treatment when compared to CPAP, and, for this reason, they would become less concerned and more relaxed when interacting with the newborn.

Concerning specific diseases, Gao et al focused on meconium aspiration syndrome and persistent pulmonary hypertension in newborns. This study disclosed that it is essential to avoid pneumothorax to reduce the incidence and mortality of persistent pulmonary hypertension of the newborn in infants with meconium aspiration syndrome and that it is also crucial to reduce the invasive ventilation time and avert weaning failure in the treatment of these 2 conditions. This study also suggested that there was a lower weaning failure rate in the HFNC group; however, there was no statistically significant difference, and studies with longer follow-up and a larger number of participants are required.

The findings of this review suggest that HFNC may be as effective and safe as CPAP, with similar extubation failure and risk of air leak syndrome, pneumothorax, BPD, and mortality with the advantage of less nasal trauma. In the very premature group, particularly in the extreme premature group, there are still some efficacy and safety concerns. More studies addressing this gestational age stratum and the noninferiority of HFNC are needed, but this method should be considered as an alternative to CPAP in postextubation settings in neonates.

**Strengths and Limitations**

This systematic review included exclusively randomized controlled trials and a significant number of patients with worldwide representation. However, there are some limitations in this review, such as the substantial heterogeneity found in some variables, the fact that not all studies analyzed all the secondary outcomes proposed, and the inclusion of a study that only analyzed term newborns with specific diseases, which contributed to greater heterogeneity.

**CONCLUSION**

High-flow nasal cannula has been increasingly used in neonatology as an alternative to CPAP. This systematic review and meta-analysis found no statistically significant differences in extubation failure, risk of air leak syndrome, pneumothorax, BPD, and mortality, but there were statistically significant differences in the incidence of nasal trauma. Therefore, HFNC may be as effective and safe as CPAP in postextubation in neonates, with the benefit of its reduced incidence of nasal trauma. However, especially in neonates born before 28 weeks, there are still some concerns about the safety and efficacy of HFNC; hence, more studies addressing this topic are required, particularly randomized controlled trials including extreme gestational ages.
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REFERENCES
1. Fleeman N, Mahon J, Bates V, et al. The clinical effectiveness and cost-effectiveness of heated humidified high-flow nasal cannula compared with usual care for preterm infants: systematic review and economic evaluation. Health Technol Assess. 2016;20(30):1–68. [CrossRef]
2. Mikalsen IB, Davis P, Øymar K. High flow nasal cannula in children: a literature review. Scand J Trauma Resusc Emerg Med. 2016;24:93. [CrossRef]
3. Hodgson KA, Manley BJ, Davis PG. Is nasal high flow inferior to continuous positive airway pressure for neonates? Clin Perinatol. 2019;46(3):20190613. [CrossRef]
4. Shehadeh AMH. Non-invasive respiratory support for preterm infants following extubation from mechanical ventilation. A narrative review and guideline suggestion. Pediatr Neonatol. 2020;61(2):20191011. [CrossRef]
5. Manley BJ, Owen LS. High-flow nasal cannula: mechanisms, evidence and recommendations. Semin Fetal Neonat Med. 2016;21(3):20160209. [CrossRef]
6. Chowdhury O, Wedderburn CJ, Duffy D, Greenough A. CPAP review. Eurr J Pediatr. 2012;171(10):20111216. [CrossRef]
7. Narasimhan R, Krishnamurthy S. A review of non-invasive ventilation support in neonates. Paediatr Child Health. 2014;24(1):7–11. [CrossRef]
8. Roberts CT, Manley BJ, Dawson JA, Davis PG. Nursing perceptions of high-flow nasal cannulae treatment for very preterm infants. J Paediatr Child Health. 2014;50(10):20140618. [CrossRef]
9. Wilkinson D, Andersen C, O’Donnell CP, De Paoli AG, Manley BJ. High flow nasal cannula for respiratory support in preterm infants. Cochrane Database Syst Rev. 2016;2:CDO06405. [CrossRef]
10. Colletti J, de Azevedo R, Araujo O, de Carvalho WB. High-flow nasal cannula as a post-extubation respiratory support strategy in preterm infants: a systematic review and meta-analysis. J Pediatr-Brazil. 2020;96(4):422–431. [CrossRef]
11. Kotecha SJ, Adappa R, Gupta N, Watkins WJ, Kotecha S, Chakraborty M. Safety and efficacy of high-flow nasal cannula therapy in preterm infants: a meta-analysis. Pediatrics. 2015;136(3):20150817. [CrossRef]
12. Manley BJ, Dold SK, Davis PG, Roehr CC. High-flow nasal cannulae for respiratory support of preterm infants: a review of the evidence. Neonatology. 2012;102(4):20120906. [CrossRef]
13. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10(1):89. [CrossRef]
14. Health NLo. Study Quality Assessment Tools; 2014; vol 2018. Available at: https://www.nhlbinihgov/health-topics/study-quality-assessment-tools.
15. Manley BJ, Owen LS, Davis PG. High-flow nasal cannulae in very preterm infants after extubation. N Engl J Med. 2014;370(4):385–386. [CrossRef]
16. Collins CL, Holberton JR, Barfield C, Davis PG. A randomized controlled trial to compare heated humidified high-flow nasal cannulae with nasal continuous positive airway pressure postextubation in premature infants. J Pediatr. 2013;162(5):949–54.e1. [CrossRef]
17. Gao XY, Feng L, Qiu YF, Pan XN. Application of humidified high-flow nasal cannula in neonates with meconium aspiration syndrome and pulmonary hypertension after extubation. Zhongguo Dang Dai Er Ke Za Zhi. 2017;19(4):393–397. [CrossRef]
18. Kang WQ, Xu BL, Liu DP, et al. Efficacy of heated humidified high-flow nasal cannula in preterm infants aged less than 32 weeks after ventilator weaning. Zhongguo Dang Dai Er Ke Za Zhi. 2016;18(6):488–491. [CrossRef]
19. Morsy RS, Badawy MMS, Said RN, Ali AA, Abuelhamd WA. A Comparative Study between postextubation of preterm Neonates into High-Flow Nasal Cannula versus Nasal Continuous positive airway pressure. Iran J Neonatol. 2021;12(1):12–19. [CrossRef]
20. Soonsawad S, Swatetsulipun B, Limrungsikul A, Nuntanarumit P. Heated humidified high-flow nasal cannula for prevention of extubation failure in preterm infants. Indian J Pediatr. 2017;84(4):20170105. [CrossRef]
21. Yengkhom R, Suryawanshi P, Gupta B, Deshpande S. Heated Humidified High-Flow Nasal Cannula vs. nasal continuous positive airway pressure for post-extubation Respiratory Support in preterm Infants: a randomized controlled trial. J Trop Pediatr. 2021;67(1). [CrossRef]
22. Collins CL, Barfield C, Horne RS, Davis PG. A comparison of nasal trauma in preterm infants extubated to either heated humidified high-flow nasal cannulae or nasal continuous positive airway pressure. Eur J Pediatr. 2014;173(2):20130818. [CrossRef]
23. Uchiyama A, Okazaki K, Kondo M, et al. Randomized controlled trial of high-flow nasal cannula in preterm infants After extubation. Pediatrics. 2020;146(6). [CrossRef]
24. Fleeman N, Dundar Y, Shah PS, Shaw BN. Heated humidified high-flow nasal cannula for preterm infants: an updated systematic review and meta-analysis. Int J Technol Assess Health Care. 2019;35(4):298–306. [CrossRef]
25. Hong H, Li XX, Li J, Zhang QZ. High-flow nasal cannula versus nasal continuous positive airway pressure for respiratory support in preterm infants: a meta-analysis of randomized controlled trials. J Matern Fetal Neonatal Med. 2021;34(2):293–266. [CrossRef]
26. Brenne H, Grunewald KH, Follstad T, Bergseng H. A randomised cross-over study showed no difference in diaphragm activity during weaning from respiratory support. Acta Paediatr. 2018;107(10):1726–1732. [CrossRef]
27. Kanbar LJ, Shalish W, Latremouille S, et al. Cardiorespiratory behavior of preterm infants receiving continuous positive airway pressure and high flow nasal cannula post extubation: randomized crossover study. Pediatr Res. 2020;87(1):62–68. [CrossRef]
28. Glackin SJ, O’Sullivan A, George S, Semberova J, Miletin J. High flow nasal cannula versus NCPAP, duration to full oral feeds in preterm infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2017;102(4):20161223. [CrossRef]
29. Charki S, Patil PK, Hadalgi L, et al. Cardiorespiratory behavior of preterm infants receiving continuous positive airway pressure and high flow nasal cannula post extubation: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed. 2017;102(4):20161223. [CrossRef]
30. Engelsland H, Johannessen B. Nurses’ experiences by using heated humidified high flow cannula to premature infants versus nasal continuous positive airway pressure. J Neonatal Nurs. 2016;22(1):21–26. [CrossRef]