High flow nasal cannula oxygen therapy in children: a clinical review

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Running title: High flow nasal cannula in children
ABSTRACT

High flow nasal cannula (HFNC) is a relatively safe and effective noninvasive ventilation that is recently accepted as a treatment option for acute respiratory support before endotracheal intubation or invasive ventilation. The action mechanism of HFNC includes a decrease of nasopharyngeal resistance, washout of dead space, reduction of inflow of ambient air, and an increase of airway pressure. In preterm infants, HFNC can be used for the prevention of reintubation and initial noninvasive respiratory support after birth. In children, adjustment of flow level is crucial under consideration of maximal efficacy and complications. Randomized controlled studies suggest HFNC can be used in moderate to severe bronchiolitis when the initial low-flow oxygen has failed. HFNC can also reduce intubation and mechanical ventilation in children with respiratory failure. Several observational studies have shown that HFNC can provide benefit in acute asthma and other respiratory distress. Multicenter randomized studies to determine the feasibility and adherence of HFNC and continuous positive airway pressure in pediatric intensive care units are warranted. The development of clinical guidelines for HFNC, including flow settings, indication and contraindications, management of device, efficacy identification, and safety issues are needed, especially in children.

Keywords: High flow nasal cannula, Noninvasive ventilation, Pediatric indication, Child
Introduction

Since the first introduction of high flow nasal cannula (HFNC) oxygenation as an alternative to continuous positive airway pressure (CPAP) in preterm infants, it has been widely used for various respiratory conditions in adults and neonates. Because of its easy application, effectiveness, and relatively good safety, HFNC is recently considered as one of the essential devices for intensive care. Indications of HFNC in preterm infants include initial noninvasive respiratory support after birth and prevention of reintubation. Although the broader indications in adults, the efficacy of HFNC in children have limitedly demonstrated after the first use in acute bronchiolitis. This review focuses on indications, flow settings, evaluation of responders, and safety of HFNC in children.

Current understanding of action mechanism

The full name of HFNC is heated humidified high-flow nasal cannula (HHHFNC) oxygen therapy. Adjustable (FiO₂ 21%~100%) heated (34°C~37°C) oxygen with nearly 100% relative humidity can avoid mucosal injury and patient discomfort possibly from cold and dry air. Heated humidification can encourage the clearance of secretion and reduce bronchoconstriction. The basic principle of HFNC is to set higher oxygen flow than inspiratory demand flow according to the clinical situations. This can lead washout of upper airways, a decrease of the nasal resistance, and reduction of dead space. Current studies revealed that HFNC induces positive airway pressure to lead alveolar recruitment of collapsed lesions and the elevation of functional residual capacity (FRC). Additionally, HFNC reduces an inflow of ambient air, then minimizes dilution of wanted gas composition, and improves oxygenation. There is no age-dependent differentiation between adults and children in the action mechanism.
Flow setting and cannula size for pediatric patients

The aforementioned principle, higher flow setting than inspiratory demand can be applied to all age of patients. Airway pressure generated from a high flow system is varying and depends on the amount of flow, the size of cannula and nares, and the degree of mouth opening in the experimental study. In the experimental setting, positive lung-distending pressure increased as the flow increase from 0 to 12 L/min. Recent studies reported that limited pressure delivery ranging from 2~4 cmH$_2$O were measured in pharynx and esophagus both in children and adults with HFNC.

There is a lack of guidance about optimal flow in pediatric patients, but some studies let us expect that. Important randomized controlled studies conducted in patients with acute bronchiolitis give us information about the appropriate flow. Patients younger than 24 months of age were tolerated to the flow of 1~2 L/kg/min (up to 20 L/min) and also to 3 L/kg/min. However, patients were uncomfortable with 3 L/kg/min despite the same efficacy.

In consideration of the flow limitation in adults (50~60 L/min), the reasonable flow rate is thought to be 1~2 L/kg/min up to 10 kg of patients and after that increase of 0.5 L/kg/min. One study comparing the efficacy of HFNC and CPAP noted no differences in the length of stay in intensive care unit (ICU), and need for mechanical ventilation between 2 L/kg/min of HFNC and 7 cmH$_2$O of CPAP. Interestingly, there was a large variation of maximal flow rates (L/min) in different age groups between 67 hospitals. These results showed the importance of a comprehensive understanding of the mechanism and optimal flow for better outcomes.

The size of the cannula is varying for age and body weight. Manufacturers recommend a cross-sectional area of the cannula should be no more than 50% that of nares because of a risk of unexpected elevation of airway pressure and following risk of air leak. That means appropriate outer diameter of cannula is no more than two third of nares diameter.
approximately. Recommended flow settings and cannula sizes for pediatric patients are summarized in Table 1.

Indications of HFNC in children (summarized in Table 2)

During recent decades, HFNC has been widely used in adult patients. Indications from the evidence in adults include acute hypoxemic respiratory failure, post-extubation support, pre-oxygenation before intubation or during bronchoscopy, postoperative respiratory failure, and acute pulmonary edema.\(^{17}\) Many pediatric studies have been published in patients with acute bronchiolitis. However, other indications have been studied, including asthma, sleep apnea, pneumonia, transport of a critical patient, and post-extubation respiratory support.\(^ {17, 18}\)

We should know contraindication of HFNC include upper airway abnormalities that may make HFNC ineffective or potentially dangerous, life-threatening hypoxia and hemodynamic instability, the trauma of facial bone or skull base, and pneumothorax. In addition, HFNC should be applied carefully in patients with a decreased level of consciousness, congenital heart disease, acute asthma, and chronic respiratory failure.

Acute bronchiolitis

Acute bronchiolitis has been the main indication of HFNC in children above neonates. The recent studies confirmed the effectiveness of HFNC as rescue therapy in the treatment of moderate to severe bronchiolitis. The first randomized controlled trial (RCT) was conducted in the patients (N=202) younger than 24 months of age with moderate bronchiolitis.\(^ {12}\) HFNC of 1 L/min/kg with 0.6 of a fraction of inspired oxygen (FiO\(_2\)) was compared with standard low flow (2 L/min). There were no differences in time on oxygen treatment and transfer rate to ICU, but a lower rate of treatment failure was found in HFNC group. Another large scale RCT in infants (< 12 months of age, N=1,472) with bronchiolitis confirmed the significantly
lower rate of treatment failure in HFNC group than those in standard oxygen group. Also, there were no differences in duration of hospital stay, duration of oxygen therapy, and ICU admission. These remarkable two RCTs concluded that HFNC has a role as rescue therapy in patients with moderately severe bronchiolitis, and physicians should remember first use of HFNC does not modify the disease process. In the recent systematic review from nine RCTs, there are no differences in length of stay, duration of oxygen therapy, ICU transfer, intubation rate, respiratory rate, SpO2 and adverse events in HFNC group compared with standard oxygen therapy and nasal CPAP group. The incidence of treatment failure in HFNC group was lower than standard oxygen group, but higher than nasal CPAP group.

Asthma

Limited data is supporting HFNC apply in children except for bronchiolitis. However, more results with clinical evidence are expected soon because HFNC is easily applied with a broad indication in adults and a definite advantage in children with bronchiolitis.

In a retrospective observational study conducted in patients with status asthmaticus (N=73), there was an improvement in pH, pCO2, heart rate, respiration rate, and oxygenation in HFNC group compared to the standard oxygen group. There was two treatment failure in HFNC group (n=39). One patient had pneumothorax and another one received other noninvasive support. Another randomized pilot trial in emergency department (ED) patients with moderate-to-severe asthma exacerbation reported an improvement in pulmonary score in HFNC group compared to the standard oxygen group at 2 hours after the treatment. In HFNC treatment for asthma, physicians have to think about optimal inhalation therapy such as a bronchodilator, anticholinergic agents, and inhaled corticosteroids. Because HFNC can reduce the entrainment of ambient air, it inhibits the optimal inhalation therapy via nebulizer. Current evidence reported that the amount of aerosol delivery was meager at in vitro high
flow system. In this situation, temporary discontinuation of HFNC or lowering the flow below 5 L/min should be considered at the time of nebulization.

Other indications

Clinical indications reported from 67 PICU and neonatal intensive care unit (NICU) in Germany include bronchiolitis, respiratory support for preterm infants, pneumonia, severe obstructive bronchitis or asthma, bridging to intubation and post-extubation support. Apnea, post-operative respiratory support, and upper airway obstruction were also reported, but the evidence-based study is lacking. In the ED, HFNC could be considered for patients with respiratory distress not requiring immediate endotracheal intubation.

In adult studies for acute respiratory failure, HFNC reduced the rate of intubation, mechanical ventilation, and the escalation of respiratory support compared to conventional oxygen therapy, but showed no better outcomes compared to noninvasive ventilation. Acute respiratory failure due to various etiology in children might be treated with HFNC before other respiratory supports according to patient severity and clinical settings. HFNC improved oxygenation with reducing heart rate in CPAP intolerant children (N=10) with obstructive sleep apnea syndrome (OSAS). Moreover, another study reported the improvement of the apnea-hypopnea index and nadir oxygen saturation in five patients with HFNC. These suggested HFNC could warrant further study and consideration as alternative OSAS therapy. HFNC therapy improved respiration rate of pediatric patients who have post-extubation acute respiratory failure after cardiac surgery. HFNC showed a lower failure rate after extubation compared with that of conventional oxygen therapy group in ICU.

Studies comparing the efficacy and safety of noninvasive respiratory supports are rare. In one RCT comparing low-flow oxygen, HFNC, and bubble CPAP for children with severe pneumonia and hypoxemia, there was no difference in the treatment failure after more than 1
hour of treatment between children supported by HFNC or bubble CPAP. This study was stopped early because of higher mortality in the low-flow oxygen group. Although there was no statistical significance in mortality between HFNC (10/79, 13%) and bubble CPAP (3/79, 4%), careful interpretation is needed because there was flow limitation of HFNC (2 L/kg/min up to the maximum of 12 L/min) in the subjects younger than 5 years. Another study comparing HFNC and helmet CPAP in children with respiratory distress aged 1~24 months reported that both were efficient in improving the respiratory distress, although the clinical response to helmet CPAP was more efficient and rapid compared with HFNC. In 2017, a randomized feasibility trial of noninvasive respiratory support (NRS) including HFNC and CPAP was conducted in critically ill children with primary respiratory failure (Group A: step up NRS) and post-extubation support (Group B: step down NRS). This pilot study showed it was feasible to conduct a large RCT in the pediatric critical care setting.

**Identification of efficacy**

Good responders to HFNC generally show improvement in respiratory rate (RR), heart rate (HR), and work of breathing (WOB) within the first 60~90 minutes. Reduction of apnea and oxygen requirement are also indicative. If the patients showed increasing oxygen requirement and unchanged or rising RR, HR, and WOB in this period, adjustment of flow rate and FiO2, another respiratory support, and ICU transfer from the ward should be considered. Non-responders in severe viral bronchiolitis were more likely to have a higher pediatric risk of mortality III scores (PRISM III). Therefore careful observation with pulse oximeter under central monitoring system is important for early detection of aggravation.

**Safety issue in children**

HFNC is generally safe in the general pediatric ward, ED, and PICU. Well known
complication of HFNC is barotrauma such as air-trapping, pneumothorax, and pneumomediastinum. Serious pneumothorax in children has been reported infrequently.\textsuperscript{33) Careful observation seems to be mandatory since this was reported even in low flow (6 L/min in 22 months old child). The use of the inappropriate large size of cannula is associated with barotrauma. Abdominal distention and nasal mucosal injury also happen. Non-adherence to HFNC is sometimes reported in children.\textsuperscript{22)}

\textbf{Conclusion}

Comparison of clinical outcomes between the pre- and the post-HFNC era was conducted in PICU.\textsuperscript{34) A significant decrease in the intubation rate and total mechanical ventilator days per admission were reported despite no associated change of mortality. Strong evidence exists in the rescue therapy for acute bronchiolitis and advantage in other indications have been reported. Better designed and controlled studies are needed for other indications and comparison with other respiratory supports. Although HFNC is a relatively safe, well-tolerated, and feasible method in a general pediatric ward, ED or ICU, careful monitoring is required for detecting non-responders and potential complications.
References


2017;5:35.


Table 1. Recommended flow settings and cannula sizes for high flow nasal cannula therapy in pediatric patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Body weight</th>
<th>Flow range†</th>
<th>Manufacturer-recommended cannula size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Fischer &amp; Paykel†</td>
<td>Vapotherm</td>
</tr>
<tr>
<td>≤ 1 month</td>
<td>&lt; 4 kg</td>
<td>5~8 L/min</td>
<td>S, M</td>
</tr>
<tr>
<td>1 month–1 year</td>
<td>4~10 kg</td>
<td>8~20 L/min</td>
<td>M, L</td>
</tr>
<tr>
<td>1~6 years</td>
<td>10~20 kg</td>
<td>12~25 L/min</td>
<td>L, XL</td>
</tr>
<tr>
<td>6~12 years</td>
<td>20~40 kg</td>
<td>20~30 L/min</td>
<td>XL, Small</td>
</tr>
<tr>
<td>12~18 years</td>
<td>&gt; 40 kg</td>
<td>25~50 L/min</td>
<td>Small, Medium</td>
</tr>
</tbody>
</table>

OD, outer diameter.

† Allowed flow range might be different from the manufacturer’s recommendations.

‡ XS, S, M, L, and XL in Optiflow™ Junior 2, Small and Medium in Optiflow™ Plus.
<table>
<thead>
<tr>
<th>Disease, conditions</th>
<th>Authors, year</th>
<th>Study design</th>
<th>Subjects characteristics</th>
<th>Main results</th>
</tr>
</thead>
</table>
| Bronchiolitis       | Kepreotes, 2017 | RCT, high flow (1 L/min/kg) vs standard flow (2 L/min) | N=202, < 24 months, moderate bronchiolitis | - Lower rate of treatment failure in HFNC group  
- No differences in duration of oxygen therapy and ICU transfer |
|                     | Franklin, 2018 | RCT, high flow (2 L/min/kg) vs standard flow (2 L/min) | N=1,472, < 12 months, moderate bronchiolitis | - Lower rate of treatment failure in HFNC group  
- No differences in duration of oxygen therapy, hospital stay, and ICU transfer |
|                     | Milesi, 2018   | RCT, high flow (2 L/min/kg) vs high flow (3 L/min/kg) | < 6 months, N=286, moderate to severe bronchiolitis | - No differences in the rate of treatment failure  
- More discomfort in group with 3 L/kg/min |
|                     | Liu, 2019      | Systematic review, 9 RCTs, HFNC vs other oxygen therapies (SOT, nCPAP) | N=2,121 | vs. SOT and nCPAP  
- No differences in length of stay, duration of oxygen therapy, ICU transfer, intubation rate, respiratory rate, SpO₂ and adverse events  
- Significant reduction of the treatment failure (RR 0.50, 95% CI 0.40 to 0.62) compared with SOT group  
- Significant increase of the treatment failure (RR 1.61, 95% CI 1.06 to 2.42)  
- Significant decreased of length of stay compared with SOT group in low-income and middle-income countries |
<p>| Asthma              | Baudin, 2017   | Retrospective observational study, HFNC vs SOT | N=73, ICU patients with status asthmaticus | - Improvement in pH, pCO₂, heart rate, respiration rate, and oxygenation in HFNC group compared to the standard oxygen group |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Interventions</th>
<th>Participants</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ballestero, 2018</td>
<td>Prospective randomized pilot trial, HFNC vs SOT</td>
<td>N=62, ED patients with moderate-to-severe asthma exacerbation</td>
<td>- At 2 hours after the start of therapy, improvement in pulmonary score in HFNC group compared to the standard oxygen group</td>
</tr>
<tr>
<td>Hawkins, 2017</td>
<td>Observational study, HFNC 10–50 L/min</td>
<td>N=10, 1–18 years old, OSAS and CPAP intolerance</td>
<td>- Improvement in obstructive apnea-hypopnea index, SpO_2, and heart rate in CPAP intolerant children</td>
</tr>
<tr>
<td>Joseph, 2015</td>
<td>Retrospective review</td>
<td>N=5, 2 months–15 years, OSAS and CPAP intolerance</td>
<td>- Improvement in apnea-hypopnea index and nadir oxygen saturation</td>
</tr>
<tr>
<td>Shioji, 2017</td>
<td>Retrospective observational study, pre-HFNC vs post-HFNC</td>
<td>N=20, &lt; 48 months, post-extubation respiratory failure after cardiac surgery</td>
<td>- Improvement in respiration rate after HFNC apply</td>
</tr>
<tr>
<td>Akyıldız, 2018</td>
<td>RCT, HFNC vs conventional oxygen therapy</td>
<td>N=100, 1 month–18 years, ICU patients after extubation</td>
<td>- Improvement in respiration rate, heart rate, end-tidal CO_2, and atelectasis in HFNC group</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Lower failure rate of extubation in HFNC group</td>
</tr>
<tr>
<td>Chisti, 2015</td>
<td>Open RCT, HFNC vs bubble CPAP vs low flow oxygen</td>
<td>N=225, &lt; 5 years old, severe pneumonia and hypoxemia</td>
<td>- No difference in the treatment failure after more than 1 hour of treatment between children with HFNC and bubble CPAP</td>
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<td></td>
<td></td>
<td></td>
<td>- Study was early stopped because of higher mortality in the low-flow oxygen group</td>
</tr>
<tr>
<td>Vitaliti, 2017</td>
<td>Prospective observational study, HFNC vs helmet CPAP</td>
<td>N=60, 1–24 months, bronchiolitis (n=31), pneumonia (n=7), asthma (n=2)</td>
<td>- Improvement of respiratory distress both HFNC and helmet CPAP group, but helmet CPAP was more efficient and rapid compared with HFNC</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; HFNC, high flow nasal cannula; ICU, intensive care unit; SOT, standard oxygen therapy; nCPAP, nasal continuous positive airway pressure