High-flow nasal cannula not proven to be superior to low-flow oxygen in the initial management of moderate bronchiolitis, but possibly a safe option as rescue treatment

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Clinical question

Are heated, humidified, high-flow nasal cannulas (HFNC), compared to conventional respiratory support, safe and effective in the treatment of infants with bronchiolitis?

Context

Bronchiolitis, often with a viral aetiology, is a major cause of hospitalization in infants < 24 months. Treatment is limited to supportive therapy, including oxygen treatment, fluid therapy and respiratory support, due to a lack of effective pharmacotherapy. Oxygen treatment is traditionally provided as a dry gas, via low-flow nasal cannulas. HFNS are able to provide oxygen flows at rates of up to 12 L/min in infants, thus providing a minimally invasive form of continuous positive airway pressure (CPAP). This is thought to reduce the need for invasive respiratory support. Observational studies suggest positive effects from HFNC.

This Cochrane review, published in 2014, assessed the effects of HFNC, defined as flows > 4 L/min, in infants < 24 months with a clinical diagnosis of bronchiolitis. The reviewers defined the need for invasive intermittent positive pressure ventilation (IPPV) or CPAP and length of hospital stay to be the primary outcomes of interest. For this Cochrane Corner, we checked if ongoing studies were published and we searched for new studies. We found two new studies for this question.

Summary of the results:

Only 1 low quality pilot study, comprising 19 participants, was identified at the time of the literature search. In this study, HFNC was compared to oxygen therapy delivered via a head-box in infants with moderate bronchiolitis. None of the children included in the study required IPPV or CPAP, while no difference could be shown between study arms regarding the length of hospital stay (median time for HFNC: 162 h (range 96-300) vs head-box oxygen therapy: 164 h (range 84 – 233), P = 0.7). No adverse events were noted in any treatment group.
In addition, the reviewers found 5 ongoing trials, to be included in future updates of the review. In the meantime, one of these trials has been published (Kepreotes 2017). Another study, not yet mentioned in the Cochrane review, has also been published recently (Milési 2017).

The study by Kepreotes et al. addressed the question whether in infants less than 24 months of age presenting at the emergency department with moderate acute viral bronchiolitis, HFNC (1 L/kg per min, with a maximum up to 20 L/min) is superior to standard therapy (100% dry oxygen delivered via a low-flow nasal cannula) as a respiratory support, and hence, could result in faster weaning from oxygen therapy. Two hundred and two infants were included in this study. Time to wean off oxygen did not differ significantly: 20 hours (95% CI 17 to 34) for HFNC versus 24 hours (95% CI 18 to 28) for standard therapy (hazard ratio 0.93, P = 0.61). Also, the length of hospital stay was similar (median time for HFNC: 2 days (IQR* 1-3) vs standard therapy: 2 days (IQR 1-3), P = 0.99). However, significantly less infants on HFNC experienced treatment failure, defined as clinical deterioration necessitating more intensive respiratory support, during the first 24 h after randomisation: 14% for HFNC versus 33% for standard therapy (hazard ratio 0.3, 95% CI** 0.2 to 0.6, P < 0.0001). About one out of 3 infants (32%) in the standard treatment group was crossed-over to HFNC as a rescue treatment. A similar proportion of infants had to be transferred to the intensive care unit (14% for HFNC versus 12% for standard treatment). No serious oxygen-related adverse events, such as pneumothorax or pressure-injuries, were observed.

The study by Milési et al. was a multi-centre trial (142 infants) testing non-inferiority of HFNC (2 L/kg per min) to nasal CPAP (7 cm H2O) in infants < 6 months of age admitted to a paediatric intensive care unit with clinically diagnosed moderate to severe bronchiolitis. The primary outcome was the proportion of treatment failures within the first 24 hours after admission, defined by pre-specified criteria for clinical deterioration. The non-inferiority margin was set at an increase in failure rate of 15% with HFNC as compared to nasal CPAP. Treatment failure occurred in 31.0% in the CPAP-group and in 51.7% in the HFNC-group (risk difference of 20%). With a 95% confidence interval of the risk difference extending from 3% up to 35%, thereby including the predefined non-inferiority margin, the conclusion regarding non-inferiority was inconclusive. However, superiority of nasal CPAP could be demonstrated with a significantly increased success rate (relative risk 1.63, 95%CI 1.02 to 2.63, p = 0.001). This means that for every 5 patients (95% CI 3 to 25) treated with nasal CPAP as opposed to HFNC, one treatment failure could be avoided. Interestingly, 82% of infants who failed nasal CPAP were successfully treated with rescue HFNC. Perhaps this is related to the finding that discomfort was the leading cause of CPAP failure. The rate of intubation (HFNC: 6.9% vs CPAP: 4.2%, RR†: 1.67, 95% CI 0.41 to 6.71, P = 0.72) and length of hospital stay (HFNC: 6.2±6 days vs 7.5±13 days, MD¤: -1.3, 95% CI -4.63 to 2.03, P = 0.44) did not differ between treatments. No serious adverse events were recorded.

Remarks:

The evidence collected in the Cochrane review was of very low quality, downgraded for limitations in study design and imprecise results. Trials not yet included in the Cochrane review were larger and of a better methodological design, with moderate to low quality evidence. The major reason for decreasing our confidence is these results is a lack of blinding, which might encompass performance bias. Furthermore the study by Milési et al. contained imprecise results.

Conclusion:

The current evidence suggests that HFNC started in infants with moderate bronchiolitis presenting at the emergency department does not result in faster weaning of oxygen therapy and a decreased length of hospital stay, compared to standard low-flow oxygen therapy.
In cases of more advanced bronchiolitis necessitating admission to an intensive care unit, nasal CPAP seems superior to HFNC as a respiratory support method. However, HFNC was not proven to be inferior to nasal CPAP.
Results from observational studies, suggesting a clear beneficial effect compared to standard low-flow oxygen therapy, do not seem to be confirmed by the currently available trials.

Implications for practice:

HFNC seems a safe and tolerable treatment option in cases of moderate acute viral bronchiolitis in young infants and could be used as a rescue therapy after failing low-flow oxygen therapy.
Infants with moderate bronchiolitis presenting at the emergency department should receive standard low-flow oxygen therapy. However, HFNC might be a safe and effective rescue therapy in case of failure of low-flow oxygen therapy. For infants with more advanced bronchiolitis: CPAP is likely to provide the best results. However, in case of failure of nasal CPAP, which is commonly due to discomfort, a rescue with HFNC seems justified.

REFERENCES:

Beggs S, Wong ZH, Kaul S, Ogden KJ, Walters JA. High-flow nasal cannula therapy for infants with bronchiolitis. Cochrane Database Syst Rev. 2014 Jan 20;(1):CD009609.

Milési C, Essouri S, Pouyau R, Liet JM, Afanetti M, Portefaix A, Baleine J, Durand S, Combes C, Douillard A, Cambonie G; Groupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP). nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). Intensive Care Med. 2017 Feb;43(2):209-216.

Kepreotes E, Whitehead B, Attia J, Oldmeadow C, Collison A, Searles A, Goddard B, Hilton J, Lee M, Mattes J. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. Lancet. 2017 Mar 4;389(10072):930-939.

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* IQR: interquartile range
** CI: confidence interval
† RR: relative risk
¤ MD: mean difference