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Extended Research Article

High-flow nasal cannula therapy versus continuous positive airway pressure for non-invasive respiratory support in paediatric critical care: the FIRST-ABC RCTs

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Scientific summary

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Scientific summary

Background

Nearly 75% of the 18,000 critically ill children admitted annually to UK paediatric intensive care units (PICUs) receive invasive or non-invasive respiratory support (NRA). NRS is used commonly in PICUs, usually to support acutely ill children with respiratory failure or to provide post-extubation support.

Although there are no randomised controlled trials (RCTs), continuous positive airway pressure (CPAP) has been widely used for NRS; however, it can be uncomfortable and associated with complications such as air leak and nasal trauma. An alternate mode of NRS, high-flow nasal cannula (HFNC), which is easy to use and is well tolerated by children, has gained popularity. The potential benefits of HFNC (patient comfort, safety profile and ease of nursing care) must be balanced against its potential risks (air leak, abdominal distension and nosocomial infection). To date, there have been no large RCTs comparing HFNC with CPAP in the PICU setting.

Following a successful pilot RCT, which supported the feasibility of performing a large pragmatic clinical trial comparing CPAP and HFNC in critically ill children, and informed its design and conduct, the FIRST-line support for Assistance in Breathing in Children (FIRST-ABC) was set up as a master protocol to answer the research question: in a child requiring NRS, either for acute illness or post-extubation support, which first-line mode of NRS is the most clinically and cost-effective treatment?

Aims and objectives

Aim

To evaluate the clinical and cost-effectiveness of HFNC when used as the first-line mode in critically ill children requiring NRS: (1) for an acute illness (step-up RCT) and (2) within 72 hours of extubation following a period of invasive ventilation (step-down RCT).

Primary objective

To evaluate the non-inferiority of HFNC, as compared with CPAP, when used as the first-line mode of NRS, both as a step-up treatment (step-up RCT) and as a step-down treatment (step-down RCT), on the time to liberation from all forms of respiratory support (invasive and/or non-invasive).

Methods

Trial design and governance

FIRST-line support for Assistance in Breathing in Children was a master protocol comprising two pragmatic, multicentre, parallel groups, non-inferiority RCTs (step-up RCT and step-down RCT) with shared infrastructure, including an internal pilot stage and integrated health economic evaluation. The trial was approved by East of England – Cambridge South Research Ethics Committee and the UK Health Research Authority. The National Institute for Health Research convened a majority independent Trial Steering Committee and an independent Data Monitoring and Ethics Committee. The trial was sponsored by Great Ormond Street Hospital NHS Foundation Trust and co-ordinated by the Intensive Care National Audit & Research Centre Clinical Trials Unit.

Participants: sites and patients

To achieve 90% power with a type I error rate of 2.5% (one-sided) to exclude the prespecified non-inferiority margin of hazard ratio (HR) = 0.75, 508 events were required to be observed. Anticipating 5% censoring for death or transfer, allowing for withdrawal/refusal of consent, and for exclusion due to non-adherence in the per-protocol population, we planned to recruit a total sample size of 600 patients in each RCT.

Children were screened and randomised if they were:

- admitted/accepted for admission to a participating PICU/high-dependency unit (HDU)
- aged > 36 weeks corrected gestational age and < 16 years
- assessed by the treating clinician to require NRS
- for an acute illness (step-up RCT)
- within 72 hours of extubation following a period of invasive ventilation (step-down RCT).

Owing to the emergency and time-sensitive nature of respiratory support, the Research Ethics Committee approved a 'research without prior consent' model, meaning that consent was sought after randomisation. Patients were randomised to HFNC or CPAP (by telephone/internet) in a 1 : 1 ratio, using permuted block sizes of 2 and 4, stratified by site and age (< 12 months vs. ≥ 12 months).

Treatment groups

High-flow nasal cannula

High-flow nasal cannula was delivered at the prescribed gas flow rates (based on patient weight) during the trial period. To standardise treatment, clinical criteria and guidance for the initiation, maintenance and weaning of HFNC were provided in a trial algorithm. As per the algorithm, patients were assessed for response to the treatment, readiness to wean and for stopping HFNC at least twice per day.

Continuous positive airway pressure

Continuous positive airway pressure could be started using any approved medical device and patient interface at a set expiratory pressure of 7–8 cm H_2O. To standardise treatment, clinical criteria and guidance for the initiation, maintenance and weaning of CPAP were provided in a trial algorithm. As per the CPAP algorithm, patients were assessed for response to the treatment, readiness to wean and for stopping CPAP at least twice per day.

Clinical practice

As the medical devices and interfaces that deliver HFNC and CPAP were easily distinguishable from each other, it was not possible to blind the patient, parents/guardians or clinical staff. Clinicians were permitted to stop HFNC/CPAP and switch to the other treatment or escalate to other forms of respiratory support, if clinically deemed necessary. Patients who switched or escalated treatments remained in the trial and continued to be monitored until liberation from respiratory support. All other usual care (e.g. sedation, feeding) was at the discretion of the treating clinical team.

Outcome measures

The primary clinical outcome was time to liberation from respiratory support. The primary cost-effectiveness outcome was 180-day incremental net monetary benefit.

Secondary outcomes included mortality at PICU/HDU discharge, day 60 and day 180; (re)intubation rate at 48 hours; duration of PICU/HDU and hospital stay; patient comfort assessed during NRS using the COMFORT Behavior (COMFORT-B) score; proportion of children in whom sedation was used during NRS; parental stress measured, in hospital at/around the time of consent at 24–48 hours, using the validated questionnaire Parental Stress Score: PICU; and health-related quality of life (HRQoL) at 180 days measured using age-appropriate Paediatric Quality of Life Inventory (PedsQL) and Child Health Utility 9 Dimension (CHU-9D) questionnaires.

Data sources

A secure, dedicated electronic case report form was used for trial data entry. To maximise efficiency, trial data were linked to the Paediatric Intensive Care Audit Network data, Hospital Episode Statistics and national death registrations (via NHS Digital). Surviving patients were mailed questionnaires at 180 days, with telephone follow-up to non-responders.

Clinical effectiveness analysis

Analyses were undertaken independently for each RCT. Analyses of primary and secondary outcomes were performed according to the randomisation group in all consented patients who commenced any respiratory support following

randomisation (primary analysis set), and in all consented patients who met eligibility criteria and commenced the randomised treatment (per-protocol analysis). Agreement of results from both analyses was required to conclude non-inferiority.

The primary analysis was performed using Cox regression to calculate a HR with one-sided 97.5% confidence intervals (CIs), adjusted for prespecified baseline covariates. *Both RCTs*: age (< 12 months vs. ≥ 12 months); SpO_2 : FiO_2 ratio; comorbidities (none vs. neurological/neuromuscular vs. other); severity of respiratory distress (severe vs. mild/moderate) and site (treated as a random factor using shared frailty). Additionally in *step-up RCT*: reason for admission (bronchiolitis vs. other respiratory vs. cardiac vs. other); and receipt of NRS at randomisation (yes/no) and in *step-down RCT*: length of prior invasive mechanical ventilation (IMV; < 5 days vs. ≥ 5 days); and reason for IMV (cardiac vs. other). HFNC was considered non-inferior to CPAP if the bound of the one-sided 97.5% CI for the adjusted HR was > 0.75 in both the primary and per-protocol analyses.

Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) was based on an NHS and Personal Social Services perspective. Total costs per patient for up to 6 months post randomisation were reported. Data from PedsQL and CHU-9D at 6 months were combined with survival data to report quality-adjusted life-years (QALYs) at 6 months. The CEA followed the intention-to-treat principle and reported the mean (95% CI) incremental costs, QALYs and net monetary benefit at 6 months. The CEA used multilevel linear regression models that allowed for clustering of patients at site. The analysis adjusted for key baseline covariates at both patient and site level.

Results

Step-up randomised controlled trial

Sites and patients

Of the 18,976 admitted children screened across 24 sites, 1449 were deemed eligible for the trial, of whom 600 (41%) were randomised between 10 August 2019 and 7 November 2021. Consent was in place for 595 children. The primary analysis set consisted of 573 children in whom respiratory support was commenced (HFNC: 295; CPAP: 278). The randomised groups had similar baseline characteristics. The median age of participants was around 9 months, 60% were male, and nearly 50% had bronchiolitis. The per-protocol analysis included 533 children (HFNC: 288; CPAP: 245); baseline characteristics were similar to the primary analysis.

Clinical management

In both groups, the allocated treatment was started in most children who started respiratory support (HFNC: 98.3% and CPAP: 88.5%). The starting HFNC gas flow rate and CPAP pressure followed the trial algorithms. Treatment failure requiring either a switch or escalation occurred in 96/290 children (33.1%) for HFNC and in 131/246 children (53.3%) for CPAP after a median of 6.1 hours (HFNC) and 4.5 hours (CPAP) following randomisation. More patients switched from CPAP to HFNC (30.9%) than from HFNC to CPAP (20.0%). Reasons for switching were mainly related to clinical deterioration in the HFNC group and to patient discomfort in the CPAP group.

Clinical effectiveness

Primary outcome

The median time from randomisation to liberation from respiratory support was 52.9 hours (95% CI 46.0 to 60.9 hours) for HFNC and 47.9 hours (95% CI 40.5 to 55.7 hours) for CPAP, with an absolute difference of 5.0 hours (95% CI −10.1 to 17.4 hours). The adjusted HR was 1.03 (one-sided 97.5% CI 0.86 to ∞). In prespecified subgroup analyses, there was a significant difference in effect between patients who were receiving respiratory support at randomisation (in whom CPAP was more effective) and those who were not. Planned sensitivity analyses did not alter the interpretation of the primary analyses.

Secondary outcomes

The rate of intubation within 48 hours was not significantly different between the groups [HFNC group: 15.4%; CPAP group: 15.9%; adjusted odds ratio (OR), 0.99; 95% CI 0.61 to 1.62]. Sedation use was significantly lower in the HFNC group (27.7% vs. 37.0% for CPAP; adjusted OR 0.59; 95% CI 0.39 to 0.88) as was duration of critical care unit stay [mean, 5 days vs. 7.4 days for CPAP; adjusted mean difference, −3.1 days (95% CI −5.1 to −1.0 days)]. The Parental Stress Score and COMFORT-B score were similar between groups.

Cost-effectiveness

At 180 days, the total costs were higher for CPAP compared to HFNC (£24,142 vs. £20,335). The HRQoL at 6 months was high but similar in both groups; the mean QALYs were slightly lower in the HFNC group. After adjustment for baseline characteristics, the estimated incremental cost of HFNC compared to CPAP was −£5702, with wide 95% CI. The cost-effectiveness plane showed most points representing incremental costs and incremental QALYs fell in the third quadrant (south-west) of the cost-effectiveness plane, indicating that HFNC resulted in lower QALYs and lower costs. At £20,000 per QALY, the incremental net benefit (INB) from adjusted analysis was positive for HFNC although with wide CIs (£5628, 95% CI −£8 to £11,264).

Step-down randomised controlled trial

Sites and patients

Out of 3121 extubated children screened in the 22 participating PICUs, 1051 fulfilled eligibility criteria and 600 (57%) were randomised between 8 August 2019 and 18 May 2020; consent was available in 587 children. The primary analysis set comprised 553 children (HFNC: 281; CPAP: 272) in whom respiratory support was started. The randomised groups had similar baseline characteristics, except for a higher proportion of children receiving ventilation for cardiac reasons in the HFNC group (28.8% vs. 20.2% in the CPAP group). The per-protocol population included 523 children (HFNC: 271; CPAP: 252); baseline characteristics were similar to the primary analysis set.

Clinical management

In both groups, most children who started any respiratory support were started with the allocated treatment (HFNC: 96.8%; CPAP: 92.6%). The starting HFNC gas flow rate and CPAP pressure were as per the trial algorithms. Treatment failure requiring a switch or escalation occurred in 101/272 children (37.1%) for HFNC and 85/252 children (33.7%) for CPAP after a median of 10 hours (HFNC) and 7.8 hours (CPAP) after randomisation. Reasons for treatment failure, particularly switch, were mainly related to clinical deterioration for HFNC and for patient discomfort for CPAP.

Clinical effectiveness

Primary outcome

The median time from randomisation to liberation from respiratory support was 50.5 hours (95% CI 43.0 to 67.9) for HFNC and 42.9 hours (95% CI 30.5 to 48.2) for CPAP (adjusted HR 0.83, one-sided 97.5% CI 0.70 to ∞). Similar results were observed in the per-protocol analysis and in prespecified subgroup analyses. Planned sensitivity analyses did not alter the interpretation of the primary analyses.

Secondary outcomes

Mortality by day 180 was significantly higher in the HFNC group: 5.6% versus 2.4% for CPAP [adjusted OR, 3.07 (95% CI 1.1 to 8.8)]. None of the other secondary outcomes, including rate of reintubation within 48 hours, were significantly different between the groups.

Cost-effectiveness

At 180 days, the total costs were higher for CPAP compared to HFNC (£30,303 vs. £28,275). The HRQoL at 6 months was high but similar in both groups; the mean QALYs were slightly lower in the HFNC group. After adjustment for baseline characteristics, the estimated incremental cost of HFNC compared to CPAP was −£4565, with wide 95% CI. The cost-effectiveness plane showed most points representing incremental costs and incremental QALYs fell in the third quadrant (south-west) of the cost-effectiveness plane, indicating that HFNC resulted in lower QALYs and lower costs. At £20,000 per QALY, the INB from adjusted analysis was positive for HFNC although with wide CIs (£4388, 95% CI −£2551 to £11,307).

Conclusions

Among acutely ill children requiring NRS, HFNC met the criterion for non-inferiority compared with CPAP for time to liberation from respiratory support, whereas in critically ill children requiring NRS following extubation, the non-inferiority of HFNC could not be demonstrated.

Implications for health care

High-flow nasal cannula is a reasonable first-line option for NRS in an acutely ill child requiring NRS. Around one in three children will fail HFNC, mainly due to clinical deterioration, and will require a switch to CPAP or escalation. On the other hand, in the post-extubation setting, CPAP is a reasonable first-line option for NRS. Around one in three children will fail CPAP, mainly due to patient discomfort.

Recommendations for research

Recommendation 1
Secondary analyses exploring patient characteristics and patterns of physiological parameters that predict treatment failure, including intubation.

Recommendation 2
Compare protocolised approaches to initiation of post-extubation respiratory support with standard care in future clinical trials.

Recommendation 3
Explore alternative approaches for evaluating heterogeneity of treatment effect both from a clinical and cost-effectiveness point of view.

Recommendation 4
Explore reasons for increased mortality in HFNC group within step-down RCT.

Study registration

Current Controlled Trials ISRCTN60048867.

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