Commentary

The FIRST-ABC Trials on non-invasive respiratory support: taking a closer look

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Abstract

MAIN TEXT: aim for 1500 to 2000 words

1. Provide an overview of why a "pragmatic trial was needed"
2. Describe the journey, with a focus of the references that ultimately got you funded
3. Describe your view of the results
4. MOST IMPORTANT: describe the pragmatic translation of the results into what you teach/do at the bedside now

How did you get from the idea to doing the actual studies – and why the need for "pragmatic" trial
Now you know the results, are you any the wiser?
Readers will really want to know what you now do as a result of the trials

Last, can you dwell on the fundamental problem – the inclusion criteria were, essentially, a bedside clinician makes a decision (but we don't know what data informs this decision):
Step-up: that the patient in front of them needs either escalation to NIV (either HFNC or nCPAP) from simple oxygen therapy
Step-down: that the patient in front of them who is about to be extubated (or has been extubated) needs some form of respiratory support beyond simple oxygen therapy (either HFNC or nCPAP)

So are the trials to be interpreted on the "prior probability" of the attendant physician considers the patient in need of something more (but not as far as ETT, yet anyway). If so, any insights as to this decision-making? Any data suggesting that all centers/clinicians behaved the same? Etc.

Non-invasive modes of respiratory support, such as high flow nasal cannula (HFNC) and continuous positive airway pressure (CPAP), are frequently used in pediatric intensive care units (PICUs) both for step-up management (i.e., providing primary respiratory support during acute illness) and step-down management (i.e, following extubation after a spell of invasive ventilation). The comparative effectiveness of HFNC and CPAP has been the subject of several observational studies in this Journal over the past decade. The relative simplicity of its setup, perceived safety and greater patient comfort has meant that HFNC has become the preferred first line mode of non-invasive respiratory support (NRS) in most respiratory (and many non-respiratory) conditions. However, until recently, there were no large randomized clinical trials (RCTs) comparing HFNC and CPAP in critically ill children.

In the first half of 2022, findings from the First-Line Support for Assistance in Breathing in Children (FIRST-ABC) trials, one comparing HFNC with CPAP for non-invasive respiratory

support in the acute setting (step-up RCT) and one in the post-extubation setting (step-down RCT), were published. In this Commentary, we were asked by the Editor-in-Chief of the Journal to provide an overview of how the FIRST-ABC trials were conceived and conducted, what our view of the results was, and how the trial findings have changed our clinical practice.

The road leading up to the trials

At the heart of every clinical trial there is an unanswered clinical question. In the case of FIRST-ABC, it was the successful use of HFNC (a novel mode of respiratory support in 2012) in a teenager with a sickle cell chest crisis that sparked the original clinical question. CPAP was the usual standard of care for managing hypoxic children with chest crises, but it was often poorly tolerated. Was HFNC an acceptable alternative to CPAP in children with respiratory failure? And what about the use of HFNC following extubation?

The road from the clinical question to the clinical trial was long (it took nearly 10 years from the idea to publishing results). It also involved a series of important, and necessary, steps: a national survey of non-invasive respiratory support use in bronchiolitis (2014), a survey of post-extubation NRS use among UK pediatric intensivists (2014, unpublished), an observational study of patterns of HFNC use in UK PICUs (2015-16), a randomised pilot trial comparing HFNC and CPAP in a mixed population of critically ill children in three UK PICUs to test the feasibility of a definitive RCT (2015-2017), and finally a successful grant application to the UK National Institute of Health Research Health Technology Assessment Programme (NIHR HTA) in 2017 for a master protocol of two trials of non-invasive respiratory support, step-up and step-down. Master protocols confer efficiency by evaluating more than one or

two treatments in more than one patient type or disease within the same overall trial structure. Each step informed the next, and built a strong narrative for the grant funder; for example, the observational study confirmed that HFNC was used in a range of diagnoses not just bronchiolitis or post-extubation, and the pilot RCT confirmed clinician willingness to randomize children into a trial and showed that the characteristics and outcomes of acutely ill children needing NRS was so different from those needing NRS post-extubation that it would not be possible to include all children into a single trial.

The choice of a pragmatic trial design

Clinical trials fall on a spectrum ranging from explanatory ('ideal-world') to pragmatic ('real-world'). The PRagmatic Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel ascertains, through responses to nine questions, where clinical trials fit on this explanatory/pragmatic continuum. FIRST-ABC was designed as a pragmatic trial for several reasons (**Figure 1** shows the PRECIS-2 wheel for the FIRST-ABC trials). First, rather than selecting children with only specific clinical diagnoses (e.g., bronchiolitis or cardiac failure), we chose to include children with all diagnoses so that trial results could be generalised to the entire population of acutely ill or extubated children. Surveys had shown that HFNC was used widely, and decisions to start HFNC were based more on clinical status rather than on the presenting diagnosis. To tease out heterogeneity of treatment effect within specific diagnostic groups, we carefully planned several subgroup analyses. Second, our inclusion criterion did not rely on any set physiological criteria – it was simply based on the clinician's decision that NRS (i.e., HFNC or CPAP) was required. While this may seem problematic considering the enormous variation in clinicians' thresholds to start NRS, the absence of robust evidence in children to support a specific threshold meant that any trial criteria we

set would be accepted by some and not by other clinicians, and many children would be started on NRS outside the trial, compromising its generalizability.

Third, rather than a prescriptive treatment algorithm, we designed trial flowcharts for the use of HFNC and CPAP that reflected real-world practice and allowed clinicians to decide when to switch between treatments or start rescue treatments, provided specific trial criteria for poor oxygenation, increase in work of breathing and/or patient discomfort were met. Fourth, FIRST-ABC was designed as a noninferiority trial (i.e., is HFNC unacceptably worse compared to CPAP?) rather than as a superiority trial (i.e., is HFNC better than CPAP?). Clinicians were willing to accept some degree of reduced efficacy of HFNC for its potential advantages; therefore, asking if HFNC was superior to CPAP did not seem the right question. Finally, based on pre-trial consultation with clinicians and parents/carers, we chose time to liberation from all forms of respiratory support as our primary outcome. Parents felt that being free of any form of breathing support, rather than just invasive ventilation, was important to them.

The main trial findings and their interpretation

Each of the trials recruited 600 children. In the step-up RCT, HFNC was shown to be noninferior to CPAP (i.e., not worse than the pre-set noninferiority margin). On the other hand, in the step-down RCT, HFNC was not shown to be noninferior to CPAP (i.e., it was worse than the pre-set noninferiority margin).

Was it surprising that the two trials showed different results? No – the population of acutely ill children requiring NRS was always likely to be different from the children requiring post-

extubation NRS, and the effect of HFNC vs CPAP was also likely to be different (indeed, our pilot RCT showed this, which is why we chose to run the two trials separately).

Does this mean that HFNC should be used as the first line mode of NRS in all acutely ill children? Almost always – the median time to liberation was 5 hours longer with HFNC than CPAP, with confidence intervals ranging from 10 hours longer to 17 hours shorter. HFNC was noninferior in all subgroups (age, diagnosis, severity of oxygenation defect and degree of respiratory distress) other than children who were already receiving NRS at randomization (mostly HFNC). Moreover, sedation use was lower with HFNC (28% vs 37%) and mean PICU length of stay was shorter (5 days vs 7.4 days). A third of children started on HFNC required rescue treatment(s) after a median of 6 hours of treatment, mostly a switch to CPAP due to clinical deterioration.

And does this mean that CPAP should be used as the first line mode of NRS in all children post-extubation? Almost always – the median time to liberation was 8 hours longer for HFNC, with confidence intervals ranging from 20 hours longer to 4 hours shorter. The only subgroup in which it might seem reasonable to start HFNC is children aged >/= 12 months, where the lower limit of the hazard ratio was 0.73, quite close to the pre-set noninferiority margin (although a hazard ratio of 0.73 represents at least 16 hours longer for time to liberation from HFNC compared to CPAP – the price to pay for the advantages of HFNC). A third of children started on CPAP required rescue treatment(s) after a median of 8 hours of treatment, mainly a switch to HFNC due to discomfort. An unexplained finding was higher mortality at 180 days in the HFNC group (5.6% vs 2.4%).

Since children were recruited based on a clinician decision rather than set physiological criteria, how easily can these results be extrapolated to other settings? Quite easily – the baseline characteristics tables display the clinical condition of the children at randomization. For example, in the step-up RCT, just over 40% of children in both groups had significant hypoxemia (SF ratio <265, corresponding to the definition of acute lung injury), and two-thirds of the children had either moderate or severe respiratory distress. Nearly 65% of the children had a respiratory rate greater than the 90th centile value for their age; in infants, this ranged between 50 and 55 breaths per minute (unpublished data). In comparison, the mean respiratory rate in the TRAMONTANE trial comparing HFNC with CPAP in severe bronchiolitis was 53 breaths per minute, and in a large observational dataset of infants with bronchiolitis from the United States, 75% of the respiratory rate values at initiation of HFNC or CPAP were >50. Importantly, observational data from UK PICUs had shown that nearly 20% of admissions received HFNC or CPAP as first line respiratory support; in the FIRST-ABC trial, out of 18,976 admissions to participating PICUs during the trial, 3825 (20%) met inclusion criteria and were started some form of NRS, indicating that practice during the trial was similar to usual clinical practice.

Translating trial findings to practice

Prior to the FIRST-ABC trials, there was little clinical trial evidence to inform clinicians regarding the best choice of first line non-invasive respiratory support. The step-up and step-down trials are the largest RCTs conducted so far in a mixed population of critically ill children, and represent a significant step forward in the field, hopefully the first of many. While some readers may disagree with the noninferiority margin chosen (i.e., some may have accepted a longer time to liberation as a trade-off for the advantages of HFNC,

whereas others may have preferred a narrower margin), and others may highlight that clinician preference for HFNC during the trial resulted in many children randomized to CPAP starting HFNC and many children switched from CPAP to HFNC for 'discomfort', the fact remains that these are methodologically sound trials which clinicians should use to inform their practice. **Table 1** summarizes the strengths and limitations of the FIRST-ABC trials.

Based on the FIRST-ABC trial findings, our current practice is to start HFNC in acutely ill children, and switch to CPAP as soon as it is evident that HFNC is failing. In the post-extubation setting, our current practice is to start CPAP as the first line mode of support in infants, and switch to HFNC if there is patient discomfort; in older children, we think that HFNC and CPAP are both equally suitable choices for first line respiratory support.

Until the next trial, that is…

Tables

Figures