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BMJ Open High continuous positive airway pressures versus non-invasive positive pressure ventilation in preterm neonates: protocol for a multicentre pilot randomised controlled trial

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ABSTRACT

Introduction Low pressure nasal continuous positive airway pressure (nCPAP) has long been the mainstay of non-invasive respiratory support for preterm neonates, at a constant distending pressure of 5–8 cmH₂O. When traditional nCPAP pressures are insufficient, other modes including nasal intermittent positive pressure ventilation (NIPPV) are used. In recent years, high nCPAP pressures (≥ 9 cmH₂O) have also emerged as an alternative. However, the comparative benefits and risks of these modalities remain unknown.

Methods and analysis In this multicentre pilot randomised controlled trial, infants <29 weeks' gestational age (GA) who either: (A) fail treatment with traditional nCPAP or (B) being extubated from invasive mechanical ventilation with mean airway pressure ≥ 10 cmH₂O, will be randomised to receive either high nCPAP (positive end-expiratory pressure 9–15 cmH₂O) or NIPPV (target mean Paw 9–15 cmH₂O). Primary outcome is feasibility of the conduct of a larger, definitive trial as assessed by rates of recruitment and protocol violations. The main secondary outcome is failure of assigned treatment within 7 days postrandomisation. Multiple other clinical outcomes including bronchopulmonary dysplasia will be ascertained. All randomised participants will be analysed using intention to treat. Baseline and demographic variables as well as outcomes will be summarised and compared using univariate analyses, and a $p < 0.05$ will be considered significant.

Ethics and dissemination The trial has been approved by the respective research ethics boards at each institution (McMaster Children's Hospital: Hamilton integrated REB approval #2113; Royal Alexandra Hospital: Health Research Ethics Board approval ID Pro00090244; Westmead Hospital: Human Research Ethics Committee approval ID 2022/ETH01343). Written, informed consent will be obtained from all parents/guardians prior to study enrolment. The findings of this pilot study will be disseminated via presentations at national and international conferences and via publication in a peer-reviewed journal. Social media platforms including Twitter will also be used to generate awareness.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Use of nasal continuous positive airway pressure (nCPAP) in preterm neonates has traditionally been limited to 8 cmH₂O; alternative non-invasive modes like nasal intermittent positive pressure ventilation are commonly used when more support is needed.
- ⇒ This protocol of a multicentre pilot trial outlines the study design and outcome measures to determine feasibility of a larger trial comparing high nCPAP (9–15 cmH₂O) versus nasal intermittent positive pressure ventilation.
- ⇒ As a pragmatic study, various aspects of clinical care, including choice of settings, devices and interfaces used will be at discretion of the clinicians.

Trial registration number NCT03512158.

INTRODUCTION

Use of non-invasive respiratory support is increasingly common in neonatal intensive care units (NICUs) to minimise dependence and duration on invasive mechanical ventilation and associated lung injury, including bronchopulmonary dysplasia (BPD).^{1 2} Data from the Canadian Neonatal Network show that the proportion of patient-days on any non-invasive respiratory mode among extremely preterm neonates has risen over the last decade, now constituting ~70% of all respiratory support.³ However, despite this paradigm shift, rates of BPD remain disappointingly high.^{4 5} It is possible that non-invasive support remains suboptimally used, particularly in convalescing infants past the initial stage of respiratory distress syndrome.

Non-invasive respiratory support most commonly consists of nasal continuous

positive airway pressure (nCPAP), which delivers a constant distending pressure traditionally set between 5 and 8 cmH₂O.⁶ Another common modality is nasal intermittent positive pressure ventilation (NIPPV), which delivers inflations ('breaths') at a set peak inflation pressure at regular intervals on top of the constant distending pressure of nCPAP, resulting in a higher mean airway pressure.⁷ In recent years, NIPPV is increasingly used, based on evidence from recent Cochrane reviews suggesting short-term benefits over nCPAP.^{8,9} However, traditional nCPAP pressures were much lower than those achieved on NIPPV in the included studies, raising the question whether benefits were the result of higher distending pressure or intermittent inflations. Moreover, most inflations delivered during NIPPV are asynchronous with patient efforts, therefore, generating minimal, if any effective tidal volume, and may lead to abdominal distension and feeding intolerance.^{7,10}

In recent years, the use of high nCPAP pressures (defined as ≥ 9 cmH₂O) is gaining popularity in some NICUs.¹¹ Given the limitations of NIPPV, high nCPAP offers an alternative that could be provided with simpler and less costly devices. While some Canadian centres have adopted its use (with 7 out of 28 sites reporting use of high nCPAP in a survey from 2017),¹¹ this has not yet translated into widespread use. Current available evidence on high nCPAP is summarised in online supplemental file. Direct comparison between high nCPAP and NIPPV using comparable mean airway pressures is lacking. Therefore, our objective is to conduct a multicentre pilot randomised controlled trial comparing high nCPAP vs NIPPV to assess the feasibility of conduct of a larger definitive trial. The long-term impact of this research is to determine the optimal use of these and other non-invasive modes in a consistent, standardised, yet patient-specific and pathophysiology-based manner, founded on strong evidence, with the goal of achieving the best possible lifelong health outcomes for vulnerable preterm neonates.

METHODS AND ANALYSIS

Study design

This multicentre pilot study is an ongoing open-label, parallel arm, randomised controlled trial. This study is currently being conducted at three neonatal centres in Canada and Australia: McMaster Children's Hospital (McMaster University, lead site), Royal Alexandra Hospital (University of Alberta) and Westmead Hospital (University of Sydney) with the possibility of additional centres joining.

Patient population

All preterm neonates with gestational age <29 completed weeks admitted to a participating centre, who meet inclusion and exclusion criteria as described below and are at least 72 hours old are eligible for randomisation.

Box 1 Non-invasive respiratory support (NRS) failure criteria

- ⇒ Fractional inspired oxygen (FiO₂) >50% or rise in FiO₂ >20% in ≤ 12 hours.
- ⇒ High CO₂ with pH <7.20 (respiratory acidosis) on arterial or capillary blood gas.
- ⇒ Increased work of breathing (with RR >80 bpm) for at least 10 min.
- ⇒ Apnoea/desaturation/bradycardia spells (>1 requiring bagging over a 4-hour period or >4/hour requiring moderate stimulation $\times 4$ hours).
- ⇒ Need for intubation related to non-respiratory pathology (this option only applicable to postrandomisation NRS failure).

Inclusion criteria (either one of)

1. Failure of traditional nCPAP (5–8 cmH₂O), based on meeting at least any one or more of predetermined non-invasive failure criteria (box 1).
2. Extubation from mean airway pressure (Paw) ≥ 10 cmH₂O.

Exclusion criteria (any one or more of)

1. Major airway or non-airway congenital malformation present at birth that directly impact the need, duration or type of respiratory support, including but not limited to: Pierre-Robin Sequence, cleft lip/palate, tracheo-oesophageal fistula, congenital heart lesion (excluding patent ductus arteriosus) that is expected to require surgical repair in the first few days-months' of life, abdominal wall defects, severe renal abnormalities impacting pulmonary growth and development in utero.
2. Suspected or confirmed genetic/chromosomal abnormality.
3. Administration of either high nCPAP (≥ 9 cmH₂O) or NIPPV for at least four continuous hours outside of study protocol.

Screening, consent and randomisation procedure

All babies born at <29 completed gestational weeks are accounted for in accordance with Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines¹² and are screened for eligibility. Parents of patients who do not meet any exclusion criteria are approached for informed consent at the earliest opportunity (consent form as in online supplemental file). Any patient who meets exclusion criteria (c) while parents are considering the study is no longer deemed eligible. For families not able to converse and/or read English, translation services will be used whenever possible to describe the study for informed consent. A subject for whom consent is obtained from parents is considered an 'enrolled subject' and identified as such to the medical team. If an enrolled subject goes on to meet either of the inclusion criteria, she/he is randomised. Randomisation occurs using a centralised electronic randomisation system (generated on REDCap by an independent statistician and stratified by centre and GA in randomly varying blocks of 4, 6 or 8, ensuring allocation concealment). Randomisation can be

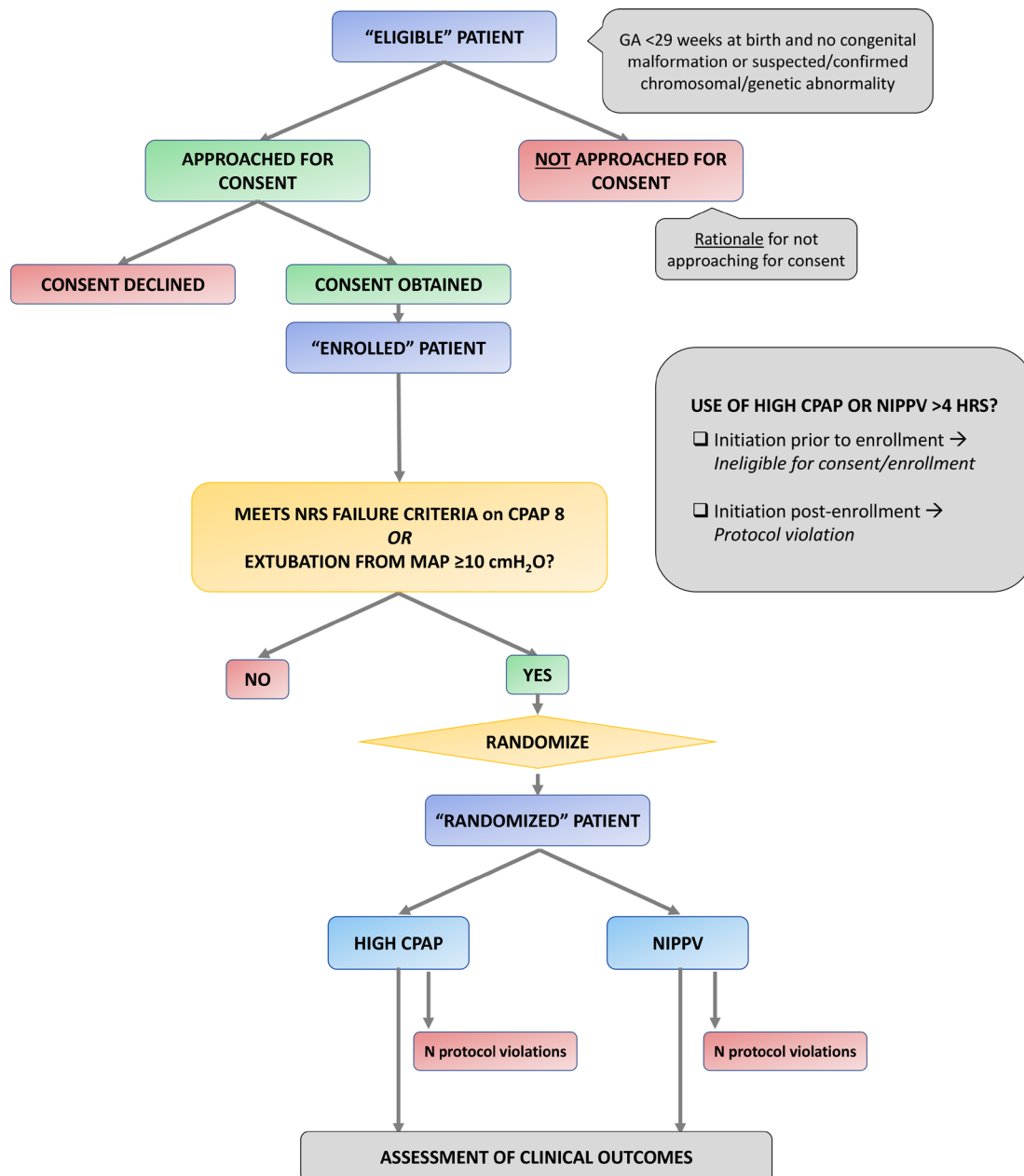


Figure 1 Schematic summarising the study process. CPAP, continuous positive airway pressure; GA, gestational age; NIPPV, nasal intermittent positive pressure ventilation.

performed either by the research coordinator or medical team. For clinical reasons, it is impossible to blind. The study schematic is summarised in [figure 1](#).

Interventions

High nCPAP

Defined as provision of nCPAP pressure between 9 and 15 cmH₂O.

NIPPV

Defined as provision of constant distending pressure with superimposed intermittent positive pressure inflations with a target mean P_{aw} between 9 and 15 cmH₂O.

Devices and Interfaces

Any ventilator device capable of generating high nCPAP or NIPPV as described is permitted with two exceptions. Synchronisation devices using diaphragmatic activity are not included, nor are devices for bilevel nCPAP. Either traditional short binasal prongs/nasal masks or the RAM cannula are permitted for study interventions.

Outcomes

Primary outcome

- Feasibility of conduct of a definitive clinical trial as assessed by all of the following at each participating site:

- i. Ability to randomise a minimum of 10% of all admitted neonates <29 weeks who do not meet exclusion criteria (A or (B)), annually.
- ii. Fewer than 20% randomised subjects with protocol violations.
- iii. Fewer than 20% of enrolled (consented, but prerandomisation) subjects with protocol violations.

Secondary outcomes: clinical

1. Failure of assigned intervention arm within 7 days postrandomisation (planned primary outcome for definitive trial)*.
2. Need for invasive ventilation within 72 hours and within 7 days postrandomisation.
3. Composite of predischarge, in-hospital mortality and/or moderate to severe BPD (NICHD 2001 criteria).
4. Predischarge, in-hospital mortality.
5. Moderate to severe BPD (NICHD 2001 criteria).
6. Duration (days) of initial hospitalisation.
7. Duration (days) of any positive pressure respiratory support.
8. Duration (days) of invasive mechanical ventilation support.
9. Duration (days) of supplemental oxygen.
10. Duration (days) of assigned intervention†.
11. Any use of invasive mechanical ventilation†.
12. Postmenstrual age (weeks) at onset of full oral feeding (without feeding tube).
13. Air leak syndromes (n, defined as pneumothorax, pneumomediastinum and/or pulmonary interstitial emphysema as defined on radiographic report)†.
14. Intestinal perforation (n, defined on radiographic report) †.

*Defined as escalation of respiratory support defined as any one of: need for intubation, escalation of settings within assigned mode beyond maximum ceiling, use of alternate NRS mode (including cross-over).

†Outcomes assessed postrandomisation only.

Postrandomisation respiratory management considerations

The assigned mode of non-invasive support based on randomisation will be used whenever necessary for the remainder of the hospital stay for each randomised subject, with no cross-over allowed. As such, a patient randomised to high nCPAP is not to be placed on NIPPV and vice versa for the duration of the hospitalisation. Guidelines for initiation and recommended increments for both intervention arms are as shown in [table 1](#), with a view towards maintaining similar mean airway pressure ranges between the two modes. Day-to-day adjustments—including weaning down to nCPAP<9 cmH₂O—will be as per the medical team. However, ceiling limits for each mode will be as follows:

- ▶ High nCPAP: maximum distending pressure level: 15 cmH₂O.
- ▶ NIPPV: maximum set peak pressure: 25 cmH₂O; or maximum positive end-expiratory pressure: 10 cmH₂O; and/or maximum mean airway pressure: 15 cmH₂O.

Postfailure management options

Whenever (and each time) a randomised subject meets non-invasive failure criteria ([box 1](#)) while on the assigned mode despite escalating settings (with a strongly suggested—but not mandated—minimum mean airway pressure of 12 cmH₂O), the clinician may exercise one of the following three options:

- ▶ Intubation and initiation of invasive mechanical ventilation.
- ▶ Escalation of settings within the randomised arm beyond the maximum ceiling limits—this will be considered failure of assigned mode.
- ▶ Use of an alternate mode of non-invasive support (eg, nasal high frequency), excluding the alternate intervention arm that is, no cross-over. However, if a cross-over is performed (see the Protocol deviation section, this will also be considered a failure of the assigned mode).

Table 1 Recommended incremental settings for high nCPAP and NIPPV

| High nCPAP | | | NIPPV | | |
|---------------------------|--------------------------|---------------------------|-------------------|--------------------|----------------|
| PEEP (cmH ₂ O) | PIP (cmH ₂ O) | PEEP (cmH ₂ O) | Fixed rate (/min) | Fixed I time (sec) | Calculated MAP |
| 9 | 13 | 7 | 40 | 0.5 | 9 |
| 10 | 14 | 8 | 40 | 0.5 | 10 |
| 11 | 17 | 8 | 40 | 0.5 | 11 |
| 12 | 18 | 9 | 40 | 0.5 | 12 |
| 13 | 21 | 9 | 40 | 0.5 | 13 |
| 14 | 22 | 10 | 40 | 0.5 | 14 |
| 15 | 25 | 10 | 40 | 0.5 | 15 |

nCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; PEEP, positive end-expiratory pressure; PIP, peak inflation pressure; PIP, peak inflation pressure.

Protocol deviations

Two major forms of protocol violations will be tracked prospectively:

1. Use of NIPPV or high nCPAP in an enrolled patient outside of trial protocol. Such patients will not be included in any further analysis of clinical (secondary) outcomes but will count towards assessment of the feasibility (primary) outcome.
2. A patient with protocol violation related to cross-over (ie, postrandomisation); such a patient will be treated as intention-to-treat for clinical outcomes, but sensitivity analyses excluding such patients will be conducted. Cross-over will also be considered to be a failure of the assigned mode.

Data abstraction and analysis plan

All patient data across participating sites will be entered directly into REDCap. Legal data sharing/transfer agreements have been completed prior to any data entry on REDCap; each site will have access to data for only patients from their own centre, except the lead investigator and study team at McMaster Children's Hospital who will have anonymised data from all centres so as to allow for conduct of analyses.

All randomised patients will be analysed using intention-to-treat principle. We will use descriptive statistics to analyse the baseline characteristics of the groups reported as Mean (SD) or Median (first quartile (Q1), third quartile (Q3)) for continuous variables depending on normality of data and count (per cent) for categorical variables. We will use descriptive statistics to analyse the feasibility outcomes reported as estimate (95% CI). For secondary clinical outcomes, we will t-test (or Wilcoxon rank sum test for non-normally distributed variables) and χ^2 test (or Fisher's exact test as appropriate) will be used to compare continuous and categorical variables, respectively. The results will be reported as estimate of effect (95% CI).

Sample size

For this multicentre pilot trial, a sample size of 100 subjects was determined based on the feasibility outcome outlined earlier (ie, ability to randomise a minimum of 10% of all patients <29 week's GA who do not meet exclusion criteria), as shown in online supplemental file. Analysis of secondary outcomes from this study will help inform the design and sample size for a larger, definitive trial.

Sensitivity analyses

The following four sets of sensitivity analyses will be conducted for secondary outcome #1 only by exclusion of:

1. Patients with at least one protocol violation due to cross-over to alternate study arm within first week postrandomisation.
2. Patients for whom a minimum MAP of 12 cmH₂O was not used prior to non-invasive support failure on at least one occasion within first week postrandomisation.

3. Patients who failed postrandomisation non-invasive support due to a non-respiratory pathology on at least one occasion within first week postrandomisation.
4. Patients placed on study intervention using RAM cannula at time of randomisation.

We will only perform sensitivity analyses if any one or more of the above results in exclusion of $\geq 20\%$ of the randomised cohort.

Results reporting

The study results will be reported in accordance with the CONSORT extension to pilot and feasibility studies.¹² The template for reporting patient flow as per CONSORT is included in online supplemental file.

Study oversight and adverse events

An independent data and safety monitoring board (comprising 2 neonatologists and 1 statistician) is performing 2 reviews—one after 30 patients, with a second review occurring after a total of 60 patients have been randomised. Details of these reviews are provided in online supplemental file.

The following serious AEs will be monitored prospectively by the research coordinator for all participating centres: (A) mortality (postrandomisation); (B) occurrence of a pulmonary air leak requiring intervention (postrandomisation and only during administration of intervention) and (C) occurrence of an intestinal perforation (postrandomisation and only during administration of intervention). Any occurrence will be reported to the DSMB by the principal investigator as well as to the research ethics board of the corresponding centre.

Patient and public involvement

The research question is driven primarily by a desire to optimise the care to patients, ultimately improving clinical outcomes. While families of patients were not involved in the design of the study, they are involved in providing continuous feedback to the recruitment and consenting process. We also have a dedicated patient advisor at the lead site involved in optimising the consenting process, liaising with both families and the study team. In addition to traditional knowledge dissemination strategies, families are given the option to provide their email address so results of the study can be shared directly.

ETHICS AND DISSEMINATION

This study proposal has been approved by the Institutional Research Ethics Board at each site: McMaster Children's Hospital: Hamilton integrated REB approval #2113; Royal Alexandra Hospital: Health Research Ethics Board approval ID Pro00090244; Westmead Hospital: Human Research Ethics Committee approval ID 2022/ETH01343. It has been conducted in accordance with the Tri-Council Policy Statement and Good Clinical Practice guidelines. Protocols are



renewed annually at each institutional ethics board, and any amendments to the protocol will be resubmitted to each institution's board for reapproval. Written, informed consent is sought from parents/legal guardians before any patient is enrolled and randomised. Subjects are deidentified on all recorded data by using unique study identification numbers and will not be identified in any knowledge dissemination or publications.

The successful conduct of a definitive clinical trial comparing high nCPAP and NIPPV is contingent on widespread dissemination of the results of this pilot study. This knowledge translation will occur at a national/international level through traditional means such as presentations at conferences (eg, Pediatric Academic Societies) and publications in peer-reviewed open-access journals for a broad readership. Online platforms such as Twitter will also be used for dissemination.

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Collaborators NOVEL Trial Group members: Melanie Amyotte, RRT; Michelle Brazil, RRT; Karen Beattie, PhD; Caroline Fray, RN; Erin Perla, RN; Melissa Luig, FRACP; Dharmesh Shah, FRACP; Hannah Skelton, BN; and Hayley McDonagh, PGCert; Steven McElroy, MD.

Contributors AM devised the study concept, wrote the protocol/grant applications and is overseeing the conduct of the study at all sites; ER is the lead study coordinator overseeing day-to-day study operations at all sites and responsible for data collection; LT is a member of the steering committee and codeveloped the analytical strategy; HJ is the study coordinator and responsible for patient enrolment at the lead site; GS, BHYL, PJ and MT are a cosite investigators at one of the sites, overseeing patient recruitment and conduct of study; CR, HK, MK and PSS are members of the steering committee and have provided methodological and analytical feedback both during the development and conduct of the study. All authors have reviewed and approved this manuscript as being submitted.

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Competing interests None declared.

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