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# A randomised trial comparing weaning from CPAP alone with weaning using heated humidified high flow nasal cannula in very preterm infants: the CHiPS study

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## ABSTRACT

**Objective** To determine whether weaning from nasal continuous positive airway pressure (nCPAP) using heated humidified high flow nasal cannula (nHF) was non-inferior to weaning using nCPAP alone in relation to time on respiratory support.
**Study design** Single-centre, non-inferiority, randomised controlled trial.
**Setting** Neonatal Intensive Care Unit, Middlemore Hospital, Auckland, New Zealand.
**Patients** 120 preterm infants, <30 weeks' gestation at birth, stable on nCPAP for at least 48 hours.
**Interventions** Infants underwent stratified randomisation to nHF 6 L/min or bubble CPAP 6 cm water. In both groups, stepwise weaning of their respiratory support over 96 hours according to a strict weaning protocol was carried out.
**Main outcome measures** Time on respiratory support from randomisation to 72 hours off respiratory support or 36 weeks' postmenstrual age. The non-inferiority threshold was set at 15%.
**Results** 59 infants were randomised to weaning using nHF and 61 using nCPAP. The groups were well balanced in regards to baseline demographics. The restricted mean duration of respiratory support following randomisation for the nCPAP group, using per-protocol analysis was 401 hours (upper boundary, mean plus 0.15, was 461 hours) and 375 hours in the nHF group (upper 95% CI 413 hours). nHF weaning was, therefore, non-inferior to nCPAP weaning at the non-inferiority threshold. There was no significant difference in time to discharge.
**Conclusion** For infants ready to wean from nCPAP, the CHiPS study found that nHF was non-inferior to discontinuing nCPAP at 5 cm water.
**Trial registration number** Australia and New Zealand Clinical Trials Registry (ACTRN12615000077561).

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Continuous positive airway pressure is the mainstay of non-invasive respiratory support in neonatal intensive care units. It does come with some complications including air leak and nasal septal damage.
⇒ Early weaning from nasal continuous positive airway pressure (nCPAP) is important, the best way to wean remains unclear.
⇒ There have only been a small number of randomised controlled trials which have explored weaning preterm infants from nCPAP using high flow nasal cannula (nHF).

### WHAT THIS STUDY ADDS

⇒ Weaning from nCPAP using nHF was non-inferior to weaning from nCPAP alone in stable very preterm infants, when using strict weaning and failure criteria.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further investigation is required into weaning extreme preterm infants born at <27 weeks' gestation off nCPAP with the use of nHF.
⇒ The study provides evidence on the use of nHF in weaning stable preterm infants from nCPAP and may help inform decision-making.

## INTRODUCTION

Nasal continuous positive airway pressure (nCPAP) has become the mainstay of non-invasive respiratory support for preterm infants.[1] Reported benefits compared with mechanical ventilation include lower rates of combined death or chronic lung disease (CLD) at 36 weeks' postmenstrual age (PMA).[2] Potential complications of nCPAP include air leak,[3] nasal septal damage[4 5] and gaseous bowel distension.[6 7] A recent study reported that despite an increase in the use of nCPAP over time, the duration of oxygen therapy and oxygen dependence at 36 weeks' PMA have risen, compared with earlier periods.[8]

Early weaning from nCPAP is, therefore, important; however, there is a lack of consensus over how best to achieve this. Options include immediate removal of nCPAP at a predetermined pressure, removing nCPAP for a number of hours each day with increasing time off and stopping nCPAP and starting high flow nasal cannula (nHF) or cycling infants between different modalities of non-invasive support.[9 10] Four randomised controlled trials (RCTs) have been published,[11–14] with the majority of these reporting that weaning from nCPAP using nHF was as effective as weaning from nCPAP alone. As well as being preferred by parents[15 16] and nurses,[17] potential benefits of nHF include easier application,[18] less nasal trauma[17 19–21] and lower rates of pneumothorax.[22] Our primary outcome was time on respiratory support.

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## METHODS

The CHiPS study was a single-centre RCT at Middlemore Hospital, New Zealand, from 2015 to 2019 (ACTRN12615000077561). Preterm infants <30 weeks' gestational age (GA) who were on Hudson (Teleflex Medical, New Zealand) bubble nCPAP 6 cm water pressure for at least 48 hours and deemed ready to wean were eligible, provided informed consent was obtained. To be deemed ready to wean infants had to meet stability criteria for the 24 hours prior to randomisation. This period could be part of the 48 hours at 6 cm nCPAP as noted above. The stability criteria were as follows:

1. No requirement for oxygen supplementation.
2. Respiratory rate ≤60 breaths/min.
3. No significant desaturation ($SpO_2$ <80%) or bradycardia (heart rate <100 beats/min) requiring bedside intervention.

Infants who had previously been off respiratory support for >7 days or had significant congenital heart disease, surgical conditions, chromosomal abnormalities, genetic syndromes or other major congenital malformations were excluded.

Prior to randomisation infants received routine clinical management, primarily bubble nCPAP using Hudson binasal prongs with humidification (Fisher and Paykel 950 humidifier, New Zealand). Prior to the study nHF using Optiflow Junior nasal prongs with humidification (Fisher and Paykel, New Zealand) was only used for infants ≥36 weeks' PMA. Airway suctioning occurred 4–6 hourly as required. All infants in the study received caffeine citrate.

The randomisation sequence was computer generated and stratified (≥27 weeks' or <27 weeks' GA) with random block sizes (2-10) and allocation using sequentially numbered sealed opaque envelopes, which clinicians opened immediately prior to study entry. Infants were randomised to wean off nCPAP support either by changing to nHF and progressively weaning the flow compared with weaning of nCPAP pressure, with strict adherence to the weaning protocol (figure 1). For all infants, the study commenced at 12 midday on the day of randomisation.

Ninety-six hours was the minimal time before trialling off. At each step stability criteria had to be met. Prior to randomisation all infants had been on nCPAP. Infants did not wean to the next step if failure criteria were met, following review of the nursing observation chart and cardiorespiratory monitor (Philips IntelliVue MX800; Philips Medizin Systeme, Germany) by the attending medical team. Failure criteria are shown in figure 1. Infants could receive increased pressure or flow if they met failure criteria and infants on nHF could be 'rescued' to nHF 8 L/min prior to being placed back on nCPAP. If nCPAP support of >6 cm water or nHF support of >8 L/min were required, then infants received rescue nCPAP until stability criteria were met and they recommenced their protocol as originally assigned. Infants who met failure criteria while off respiratory support recommenced weaning from step one of their originally assigned weaning arm. All infants were eligible for weaning again at 12:00 hours (see figure 1). Infants completed weaning by successfully remaining off respiratory support at 72 hours or reaching 36 weeks' PMA (when our usual practice was to commence low flow oxygen).

The primary outcome was the duration of respiratory support (in hours) from randomisation until weaning was completed. Secondary outcomes were subgroup analysis of the duration of respiratory support for infants <27 weeks' GA, CLD defined as any respiratory support or oxygen at 36 weeks' PMA,[23] nasal trauma (modified Fischer nasal trauma grading),[5] age of first sucking feed, age when full sucking feeds was achieved (eight consecutive sucks with no top-ups), type of feeding at discharge, weight z scores[24] and other neonatal morbidities (all defined as per local network guidelines).[23] A validated parental stress and perception of infants' treatment survey (Parental Stress Scale:-Neonatal Intensive Care Unit, PSS:NICU)[25] was given to parents at week 1 following randomisation and again at 36 weeks' PMA. Infants discharged prior to 36 weeks' PMA or those infants randomised after 34 weeks' PMA only received one survey to complete.

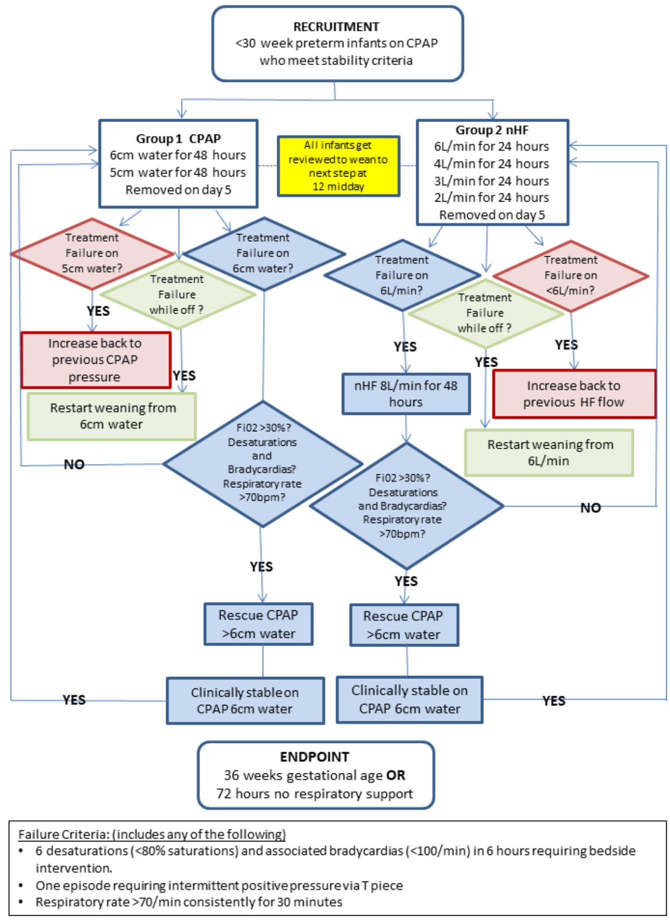



**Figure 1** Weaning protocol. nCPAP, nasal continuous positive airway pressure; nHF, high flow nasal cannula.

The study was approved by the Northern A Health and Disability Ethics Committee (15/NTA/42) and local research committees. Informed written consent was gained from the parents when infants were approaching the predetermined stability criteria.

### Statistical analysis

Sample size was determined by using observational data and bootstrapping (further described in the online supplemental file). A total of 100 infants (50 per arm) would provide a 92% power to conclude non-inferiority of the weaning time (one-sided significance test). A non-inferiority margin of 15% was chosen. To achieve the required sample size, it was planned to recruit 120 infants (60 per group).

Statistical analysis was performed using R V.3.6.1.[26] A non-inferiority one-sided alternative (significance level 2.5%) was used to test the primary hypothesis and a superiority two-sided alternative for secondary hypotheses.[27]

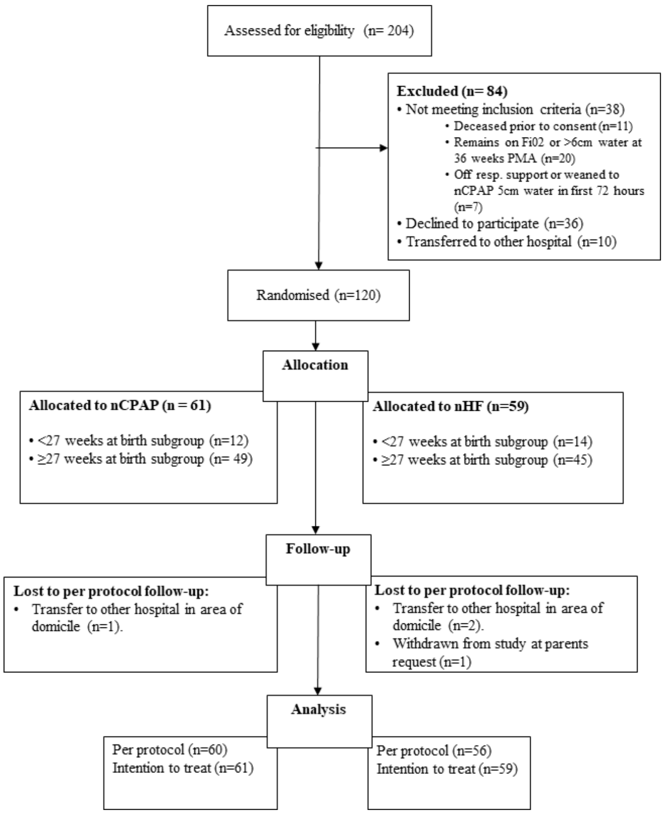



**Figure 2** Consort diagram. Fio2, fractional inspired oxygen; nCPAP, nasal continuous positive airway pressure; nHF, high flow nasal cannula; PMA, postmenstrual age.

Independent predictors were investigated (gestational age at birth, patent ductus arteriosus, late-onset sepsis, maternal diabetes and a sibling factor which identified pairs of siblings). No interactions were included in the primary outcome model. Hours on respiratory support and gestation at birth were predictors included in time to suck analyses, and gestation at birth and a sibling factor for CLD analyses.

The primary outcome was analysed using a per-protocol (pp) analysis with time-to-event (survival) analysis including right censoring for those infants who remained on respiratory support at 36 weeks' PMA (see online supplemental file for more detail). A restricted mean survival time was used for the primary outcome.[28] To obtain this, a standard survival curve was estimated. A cut-point was chosen,[29] by estimating the hazard at each event time, and searching for a point with the smallest sums of squared error for a model. This conservative approach allowed for different hazards between the two groups and the same hazard after the chosen time point.[29] Subgroup analysis of <27 weeks' GA infants was carried out in the same way. Treatment failure for example, failure of weaning, and other proportions were analysed using $\chi^2$ tests. There was no adjustment for missing outcome values. The PSS:NICU[25] consists of four domains and a total score and was analysed using linear mixed modelling with Tukey correction. The data were collected from parents over two time points.

## RESULTS

Two hundred and four infants were assessed for eligibility and 120 randomised; 61 to the nCPAP group and 59 to the nHF group. Four infants were excluded from the pp analyses, three transferred to other hospitals and one infant was withdrawn for parental request (figure 2). Of the 36 infants whose parents declined the study, there were no significant differences in important demographics compared with those randomised. Baseline demographics are shown in table 1.

### Primary outcome

PP analysis of the primary outcome (duration of respiratory support following randomisation) is shown in figure 3, and the cut-point for the restricted mean was 888 hours. The restricted mean hours from randomisation to 72 hours off respiratory support or 36 weeks' PMA was 401 hours in the nCPAP group giving an upper bound of 461 hours (mean plus 0.15 non-inferiority margin). The restricted mean in the nHF group was 375 hours with an upper CI of 413 hours, showing that nHF weaning was non-inferior to nCPAP weaning using the 15% non-inferiority margin (figure 3). An intention-to-treat analysis gave similar results (see online supplemental file).

Thirty-two infants completed the primary outcome at 96 hours (15 nHF, 17 nCPAP). It can be seen in the survival curve (figure 3) that both arms did not diverge at this early stage.

### Weaning

The first trial off respiratory support following randomisation was at a similar PMA in the two groups (median 31 weeks). On point estimates prior to successful trial off support suggested infants in the nHF group had a higher rate of escalating flow/pressure (52.5% vs 34.4%; OR 1.53 (95% CI 0.78 to 2.95)), however this was not statistically significant. Similarly, point estimates suggested reduced treatment failures prior to achieving 72 hours in the nHF group compared with nCPAP (24% vs 47.5%; OR 0.49 (95% CI 0.24 to 1.03)). The leading cause of treatment failure in both groups was desaturation/bradycardia. See table 2 for more detail.

### Secondary outcomes

In the <27 weeks' GA subgroup, we were unable to conclude nHF non-inferior to nCPAP when weaning from nCPAP within a 15% non-inferiority margin (see online supplemental file for detail). Other secondary outcomes are listed in table 2. Infants in the nHF arm had significantly less CLD than those in the nCPAP arm (18% vs 36%; OR 0.42 (95% CI 0.18 to 0.99 corrected for gestation and sibling factor but not multiple comparison)). Other secondary outcomes listed in table 2 were not significantly different. There was a 95% return for the first PSS:NICU[25] and a 77% (nCPAP) and 66% (nHF) return for the second PSS:NICU survey. Stress scores were reduced in the nHF group, in regards to the 'relationship' section of the survey ($p=0.045$; see online supplemental file and supplemental eTable for further discussion).

## DISCUSSION

Weaning from CPAP is important—there are potential adverse outcomes for weaning too slowly (exposure to oxygen, CLD) but also for weaning too rapidly, for example, atelectasis, loss of functional residual capacity and inflammation.[30] There remains a lack of consensus over how best to wean from CPAP.

Prior to this study, our usual nCPAP weaning strategy was to remove nCPAP once infants were stable in room air at a pressure of 5 cm water.[31–33] We did not use lower pressures or cycling. A systematic review of nCPAP weaning indicated that this method of abrupt cessation significantly reduced the PMA of successful weaning.[34–36] For a non-inferiority weaning study with the

**Table 1** Baseline maternal and infant characteristics

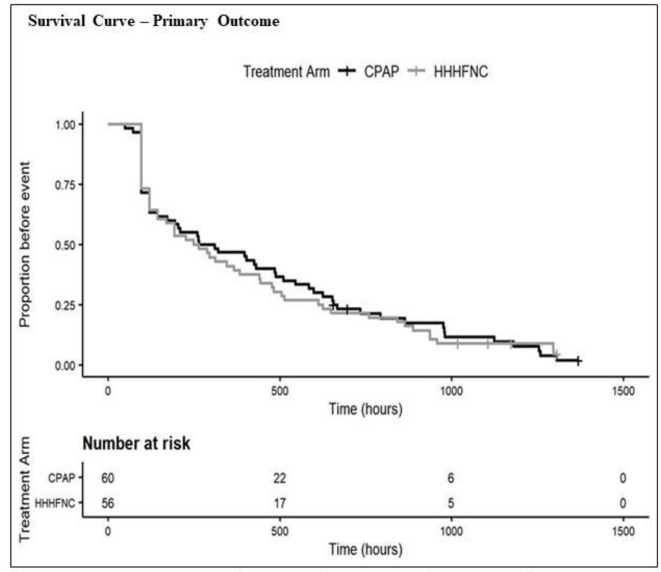
| | High flow (n=59) | nCPAP (n=61) |
|---|---|---|
| Gestational age, weeks | 28 (27–29) | 28 (27–29) |
| <27 weeks' gestation at birth | 14 (23) | 12 (19) |
| Birth weight (g) | 1115 (932–1347) | 1132 (965–1290) |
| Male | 26 (44) | 34 (55) |
| Ethnicity | | |
| New Zealand European | 6 (10) | 9 (14) |
| Māori | 21 (35) | 18 (29) |
| Pacific Peoples | 16 (27) | 21 (34) |
| Asian | 13 (22) | 13 (21) |
| Other | 3 (5) | 0 (0) |
| Multiple birth | 9 (15) | 14 (23) |
| Apgar score at 5 min | 8 (7–9) | 8 (7–9) |
| Antenatal corticosteroids | | |
| Completed | 34 (57) | 48 (78) |
| Prolonged rupture of membranes (≥18 hours) | 11 (19) | 19 (31) |
| Chorioamnionitis* | 22 (37) | 21 (34) |
| Antepartum haemorrhage | 20 (33) | 25 (41) |
| Maternal pre-eclampsia | 10 (16) | 12 (19) |
| Maternal diabetes mellitus | 8 (13) | 5 (8) |
| Emergency caesarean section | 35 (59) | 40 (65) |
| Resuscitation at birth | | |
| Intermittent positive pressure ventilation | 39 (66) | 34 (55) |
| Intubation | 14 (23) | 5 (8) |
| Chest compressions | 4 (6) | 0 (0) |
| Emergency central lines and epinephrine | 1 (1) | 0 (0) |
| Minimal one dose surfactant received | 30 (51) | 28 (45) |
| Clinical Risk Index for Babies (CRIB II) score | 7 (5.5–9) | 7 (5–9) |
| Prerandomisation | | |
| Patent ductus arteriosus requiring medical treatment | 5 (8) | 5 (8) |
| Early onset sepsis† | 0 (0) | 0 (0) |
| Mechanical ventilation | 20 (34) | 12 (20) |
| Time on mechanical ventilation (hours) | 41 (20–128) | 57 (29–186) |
| Time on nCPAP 7–9 cm water (hours) | 105 (40–310) | 72 (27–284) |
| Postmenstrual age at randomisation | 30 (29–32) | 30 (29–31) |

Data shown as median (IQR) or number (%).
*Defined on histology by pathologist.
†Australia and New Zealand Neonatal Network definition 2015.
nCPAP, nasal continuous positive airway pressure.

primary outcome being time of respiratory support, we chose a weaning method that resulted in the shortest time on support.

Owing to the potential benefits of nHF (ease of application, earlier introductions of suck feeds), our study design was a non-inferiority one—we reasoned if nHF weaning was non-inferior to our usual nCPAP weaning strategy, the other potential health benefits could make it a viable weaning tool.

We noted infants were more likely to wean successfully on the first occasion following the stepwise decrease in nHF rather than abrupt nCPAP cessation. This has been noted in other studies[35] and may reflect the more graded steps carried out with nHF weaning. Although a similar gradation could be achieved with nCPAP, such an approach has not been shown to reduce the PMA at which nCPAP is discontinued.[36] On the other hand, before




| Per protocol analysis | Restricted mean time | 15% non-inferiority margin | Upper confidence interval | Upper bound of non-inferiority margin |
|---|---|---|---|---|
| **Primary Outcome (hours)** | | | | |
| nCPAP | 401 | 60 | - | 461 |
| nHF | 375 | - | 413 | - |
| **Subgoup: <27 week GA (hours)** | | | | |
| nCPAP | 304 | 46 | - | 350 |
| nHF | 362 | - | 408 | - |

**Figure 3** Time-to-event curves for nCPAP and heated humidified high flow groups with primary outcome data using restricted mean survival time analysis. GA, gestational age; HHHFNC, heated humidified high flow nasal cannula; nCPAP, nasal continuous positive airway pressure; nHF, high flow nasal cannula.

being ready to trial off, infants on nHF required more interventions (increases in flow) than those on nCPAP; therefore, there was no overall difference in PMA at successful wean when comparing the two groups. Optimal nHF and nCPAP weaning might involve different mechanisms, but we found the overall time on support was similar. It is of interest that the PMA of nCPAP successful wean for infants <30 weeks' GA has remained constant in our centre over the past 15 years, with this PMA reflected in a systematic review.[37] Similar percentages (approximately 25%) in each group were successfully weaned off immediately after the initial 96 hours. In a post hoc analysis (see online supplemental file 1), we found that assuming the nCPAP group might have come off earlier for example, by 24 hours instead of 96 hours, did not alter the overall results.

There have been four published RCTs reporting on nHF as a strategy for weaning from nCPAP.[11–14] There is considerable heterogeneity between these studies. Abdel-Hady *et al*[13] and Badiee *et al*[12] focused on duration of oxygen requirement and included infants born >28 weeks' GA (mean 31 weeks' GA). Infants were eligible for randomisation when they reached nCPAP 5 cm water in <0.30 fractional inspired oxygen, at which time they were randomised to a fixed nHF flow of 2 L/min or remained on nCPAP 5 cm water and weaning of oxygen was commenced. One study found the use of nHF lengthened time of exposure to oxygen and respiratory support[13] and the other found a significant reduction in oxygen exposure using nHF and earlier time to discharge.[12]

Tang *et al*[11] reported no significant difference in days on respiratory support when nHF was used to wean from nCPAP . Soonsawad *et al*[14] reported that time to wean off nCPAP with

**Table 2** Weaning and secondary outcomes

| | nHF (n=59) | nCPAP (n=61) | OR (95% CI) or median difference and 95% CI* |
|---|---|---|---|
| Postmenstrual age at first trial off respiratory support, weeks | 31 (30–32) | 31 (30–33) | 0 (–1 to 0)* |
| Treatment failure occurring during 72 hours off respiratory support† | 14 (24.1) | 29 (47.5) | 0.49 (0.24 to 1.03) |
| Requirement for increase flow/pressure† | 31 (52.5) | 21 (34.4) | 1.53 (0.78 to 2.95) |
| Requirement for rescue to CPAP>6 cm water† | 13 (22.4) | 12 (19.7) | 1.12 (0.47 to 2.65) |
| Total number of infants who had any treatment failures | 35 (59.3) | 35 (57.4) | 1.03 (0.57 to 1.86) |
| Escalation for† | | | |
| Six desaturations/bradycardias in 6 hours | 23 (65.7) | 23 (65.7) | 1.03 (0.52 to 2.04) |
| Tachypnoea | 22 (62.8) | 21 (60) | 1.08 (0.54 to 2.17) |
| Increase oxygen >0.30 | 5 (14.2) | 4 (11.4) | 1.29 (0.33 to 5.05) |
| Intermittent positive pressure ventilation | 1 (2) | 1 (2) | 1.03 (0.06 to 16.9) |
| Other‡ | 3 (8.6) | 0 (0) | 3.1 (0.31 to 30.67) |
| Postmenstrual age at completed primary outcome, weeks | 33 (31–35) | 33 (31–35) | 0 (–0.7 to 0.8)* |
| Did not complete primary outcome of 72 hours off respiratory support by 36 weeks' PMA | 6 (10.2) | 12 (19.7) | 0.51 (0.18 to 1.46) |
| Time to first suck feed, restricted mean days§ | 38.6 | 39.1 | 0.63¶ |
| Time to full suck feed, restricted mean days§ | 65 | 66.2 | 0.35¶ |
| Discharged home exclusive breast feeding | 12 (21) | 13 (22) | 0.95 (0.40 to 2.26) |
| Discharged home with feeding tube | 13 (22) | 12 (20) | 1.12 (0.47 to 2.65) |
| Z-score change in weight (randomisation to discharge) | 0.18 (±0.60) | 0.22 (±0.79) | 0.19 (0.41 to –0.02)**†† |
| Age at discharge, days | 79 (63–86) | 78.5 (69–98) | 4 (-5 to 11)* |
| Necrotising enterocolitis | 0 (0) | 2 (3) | 0.97 (0.92 to 1.01) |
| Chronic lung disease†† | 11 (18) | 22 (36) | 0.42 (0.18 to 0.99) |
| Late-onset sepsis | 6 (10) | 8 (13) | 0.77 (0.25 to 2.37) |
| Retinopathy of prematurity: stage 3 | 1 (1.7) | 3 (5) | 0.34 (0.03 to 3.4) |
| Intraventricular haemorrhage: grade 3/4 | 1 (1.7) | 0 (0) | 1.02 (0.98 to 1.05) |
| Nasal trauma | 2 (3) | 4 (6) | 0.51 (0.09 to 2.9) |
| Discharged home on low flow oxygen | 6 (10.2) | 5 (8.2) | 1.24 (0.5 to 4.28) |

Data are shown as median (IQR) or number (%) unless stated otherwise.
†Infants could meet failure criteria more than once during the primary outcome period (randomisation—72 hours off respiratory support) and could fail due to more than one reason.
‡Decision made at doctors' discretion outside of protocol.
§Corrected for hours on respiratory support and gestation at birth.
¶P value.
**Z-score change.
††Corrected for sibling factor and gestation at birth.
nCPAP, nasal continuous positive airway pressure; nHF, high flow nasal cannula; PMA, postmenstrual age.

the use of nHF was not different than weaning directly from nCPAP. Both the latter studies included infants born <28 weeks' GA. In our cohort of infants <27 weeks' GA, the non-inferiority threshold for our primary outcome was not met. This may be a reflection of the small numbers but requires further research as the study was not powered for this outcome and the analysis was exploratory.

Parents in the CHiPS study reported less stress in regards to the 'relationship' section of the survey, which included separation, contact and interaction with their infant while on nHF compared with nCPAP. This is similar to another study, where parents assessed nHF treatment as significantly better than nCPAP in three survey domains: child satisfied, parental contact and interaction and possibility to take part in care.[16] Our PSS:NICU was an exploratory analysis, and the study was not powered for these outcomes.

Nasal trauma was uncommon in both groups. We did note a significant decrease in CLD in the nHF group. We did not find differences in either antenatal demographics or indicators of disease severity between groups to explain these results. However, the results are exploratory as the study was not powered for this outcome and adjustments were not made for multiple comparisons.

Strengths of the CHiPS study include a clear weaning algorithm, predetermined failure criteria, inclusion of infants with a GA of <27 weeks and the ability for nHF groups to be 'rescued' to nCPAP. The limitations include the fact that there were a small number of infants <27 weeks' GA. The study was undertaken in one NICU and the weaning occurred at a set time of day. This could lengthen time on respiratory support for some infants, although the same limitation applied to both groups. Fifteen per cent of study infants were not able to be weaned from support during the study period.

The CHiPS study validates the use of nHF as a viable alternative method for weaning preterm infants from nCPAP when using predefined stability and failure criteria.

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**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information. Study data is not available

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# Supplementary material

## 1. Supplemental Appendix One – Weaning Methods

Infants who had been off respiratory support for >7days were part of the exclusion criteria for the CHiPS study. Seven days was chosen as a cut off as infants who had to go back on respiratory support after this period were deemed likely to have an intercurrent illness or event, rather than to have failed primary weaning. Infants off respiratory support for <7days who then required respiratory support were, however, eligible for the study, and were placed on nCPAP for at least 48 hours prior to randomisation.

For all infants the study commenced at 12 midday on the day of randomisation with weaning as follows:

1. nCPAP arm: Weaned over 96 hours (all changes at 12 midday). Day 1 and 2 remained on nCPAP 6cm water (48 hours), day 3 reduced to nCPAP 5cm water for a further 48 hours. Day 5 off nCPAP at 12 midday.
2. nHF arm: Weaned over a period of 96 hours (all changes at 12 midday). Day 1 commenced on nHF flow 6L/min, Day 2 4L/min, Day 3 3L/min, Day 4 2L/min. Day 5 off nHF at 12 midday.

Failure criteria included any of the following: 6 desaturations (<80% saturations) and associated bradycardias (<100/min) in 6 hours requiring bedside intervention, one episode requiring intermittent positive pressure via T piece, or respiration rate >70/min consistently for 30 minutes.

## 2. Supplemental Appendix Two – Statistical Analysis

Observational data obtained over a 10-year period for 310 infants <30 weeks GA was used as pilot data. Review of the pilot data showed that over 80% of cases came off nCPAP in the 4 to 5 weeks between PMA of 31 and completion of 34 weeks PMA. This was regarded as the time of active weaning and was taken into account in the simulation models.

A bootstrap method was used for each set of study parameters ie: sample, size, effect size and non-inferiority threshold. Four hundred bootstrap samples with replacement were drawn from the data. From the 400 samples the proportion which would have concluded in non-inferiority using one-sided (2.5%) confidence intervals based on a heteroscedastic least-squares model was determined. These computations yielded the estimated power of each model and indicated a total of 100 infants (50 per arm) would provide a 92% power to concluded non-inferiority of the weaning time between the two methods of respiratory support. A non-inferiority margin of 15% was chosen. For nHF weaning to be shown to be non-inferior to nCPAP weaning, the mean time in the nHF arm plus the 15% non-inferiority margin would need to lie within the 95% confidence interval of the nCPAP weaning time. For a mean birth gestation of 29 weeks, the model indicated that this 15% margin amounted to a difference of approximately 4 days.

The primary outcome was analysed using a per protocol (pp) analysis. This was chosen as in the context of a non-inferiority trial it is likely to be a more conservative estimate. However, it was also planned to present the intention to treat analysis as a secondary analysis and discuss any differences that might be detected. Data was analysed as hours on respiratory support (rather than days) to avoid the problem of interpreting incomplete days.

The Restricted Mean Survival Time (RMST) comparison was used to analyse the primary outcome. It is a widely used and well described alternative time-to-event analysis method. It accommodates censoring but is not specific to censored data. The basic assumption behind RMST is that hazards in both arms may converge at some point and that to detect the difference between interventions; one should look at differences before such a point of convergence. RMST is conservative in a non-inferiority setting, as it does away with the portion of the follow-up where interventions behave similarly. RMST focuses on duration rather than hazard, which has greater relevance to the study. RMST does not assume proportionality of hazards. In order to obtain the RMST a survival curve was estimated through standard survival analysis. The cut-point was selected using the modified Sheldon hazard method, (1) which estimated the hazard at each event time and then searched for a point which gave the smallest sums of squared error for a model. This allowed for different hazards between the two groups and the same hazard after the chosen time point.(1) This method was chosen as, per the Sheldon reference above, competing methods underestimate the cut-point, potentially washing out the differences in restricted mean durations. This is why, in a non-inferiority setting we settled on this procedure for the cut-point selection.

Time on the study methods of support was not available for all as clinically at 36 weeks PMA, infants who are still on pressure support such as nCPAP or nHF are changed to low flow oxygen instead. This is because infants on nCPAP cannot establish suck feeds and use of oxygen at this later period after birth does not cause deleterious effects whereas before this all reasonable attempts are made to avoid oxygen if possible. Therefore, at 36 weeks PMA, the 2 study arms effectively cease and oxygen is given.

A subgroup analysis of time on respiratory support for infants born at <27 weeks GA was planned. The data was subject to the same procedure as for the primary outcome above and a cut-point was similarly determined.

The PSS: NICU survey which is one of the secondary outcomes consisted of four domains and a total score. The score ranged on a continuous scale (0-100); this was analysed using linear mixed modelling and empirical sandwich estimators that adjust for the standard errors and test statistics involving the fixed-effects model. A parent factor was regarded as a random effect. Interactions between group and time were investigated across the 4 domains and the total score. A Tukey test was used for multiple comparisons within the PSS:NICU.

## 3. Supplemental Appendix Three - Results

Twenty infants with more severe evolving CLD did not meet our inclusion criteria, and therefore were not included.

Using intention to treat analysis, the restricted mean hours from randomisation to 72 hours off respiratory support or 36 weeks PMA was 409 hours in the nCPAP group giving an upper bound of 470 hours (mean plus 0.15 non-inferiority margin), and 390 hours in the nHF group with an upper confidence interval of 435 hours. These results supported the findings of non-inferiority reported in the per protocol analysis (Figure 3 in article).

A post hoc analysis indicated that if it was assumed the nCPAP group could have come off support at 24 hours instead of 96 hours, this did not significantly change the time on support. The median difference between groups in this case was -23 hours (95%CI -72 to 83 hours) with the shorter median time in the nHF group.

In our subgroup analysis of our <27 week GA infants we were unable to conclude nHF non-inferior to nCPAP when weaning from nCPAP within a 15% non-inferiority margin. The cut point was selected using the Sheldon hazard method(1) and for this sub-group was 504 hours. The restricted mean time from randomisation to wean off respiratory support in the nCPAP group was 304 hours with an upper boundary of 350 hours (mean plus 0.15 margin) and when weaning using nHF this was 362 hours with an upper confidence interval of 408 hours.

Results from the PSS:NICU(2) showed stress scores were reduced in the nHF group, in regards to the 'relationship' section of the survey (p=0.045) which assesses parents perceptions on separation, contact and interaction, but increased in both groups in the sights and sounds section, over time (p=0.005). Although the total PSS:NICU score did not show significant interaction between group and time, the interaction terms were retained for each domain as it was felt likely that parents' perceptions would likely change with time in regard to some of the categories of the questionnaire.

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**eTable: PSS:NICU Survey**

| **Domains** | **Variables** | **Estimates** | **Standard Error** | **p-value*** |
|---|---|---|---|---|
| TOTAL: Sights and Sounds | Group (ref=Not High Flow) | -0.437 | 0.766 | 0.542 |
| | Time (ref=1 week) | 1.308 | 0.588 | **0.005** |
| | Interaction (Group:Time) | 0.0004 | 0.912 | 0.9996 |
| TOTAL: Baby looks and behaves | Group (ref=Not High Flow) | 2.754 | 3.875 | 0.403 |
| | Time (ref=1 week) | 0.654 | 2.693 | 0.533 |
| | Interaction (Group:Time) | 1.133 | 3.900 | 0.772 |
| TOTAL: Relationship | Group (ref=Not High Flow) | 0.187 | 1.952 | 0.374 |
| | Time (ref=1 week) | 0.282 | 1.056 | 0.086 |
| | Interaction (Group:Time) | -3.785 | 1.853 | **0.045** |
| TOTAL: Communication | Group (ref=Not High Flow) | 1.357 | 1.977 | 0.534 |
| | Time (ref=1 week) | 1.730 | 1.154 | 0.171 |
| | Interaction (Group:Time) | -0.302 | 2.285 | 0.895 |
| Overall Total | Group (ref=Not High Flow) | 3.884 | 7.200 | 0.792 |
| | Time (ref=1 week) | 4.199 | 3.968 | 0.472 |
| | Interaction (Group:Time) | -3.861 | 6.282 | 0.541 |

*Tukey's test used for multiple comparisons