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TITLE
Biphasic Positive Airway Pressure or Continuous Positive Airway Pressure: A Randomized Trial

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Short title
BiPAP vs CPAP

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The authors have no conflicts of interest relevant to this article to disclose.

Trial Registration
Current Controlled Trials ISRCTN18921778

Abbreviations

n-BiPAP	: nasal-Biphasic Positive Airway Pressure
n-CPAP	: nasal-Continuous Positive Airway Pressure
InSURE	: Intubation-Surfactant-Extubation
ITT	: Intention to Treat
NIPPV	: Non-Invasive Positive Pressure Ventilation
MAP	: Mean Airway Pressure
PDA	: Patent Ductus Arteriosus

What's known on the subject
There have been few published trials to date directly comparing the efficacy of nasal biphasic positive airway pressure (n-BiPAP) with nasal continuous positive airway pressure (n-CPAP) in preterm infants born before 30 week's gesatation and less than two weeks old.

What this study adds
This trial provides clear and conclusive evidence that n-BiPAP confers no significant benefit over n-CPAP in preventing extubation failure when used at equivalent mean airway pressures in preterm babies born before 30 weeks' gestation and less than two weeks old.

Contributors' Statement Page

Suresh Victor conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and approved the final manuscript as submitted

Stephen A Roberts helped design the study, coordinate and supervise data collection, carried out the analyses, critically reviewed and revised the manuscript, and approved the final manuscript as submitted

Simon Mitchell helped design the study, critically reviewed and approved the final manuscript as submitted

Huma Aziz helped design the study, critically reviewed the manuscript, and approved the final manuscript as submitted.

Tina Lavender helped design the study, critically reviewed the manuscript, and approved the final manuscript as submitted

ABSTRACT

Background

There is currently no clear evidence that nasal biphasic positive airway pressure (n-BiPAP) confers any advantage over nasal continuous positive airway pressure (n-CPAP). Our hypothesis was that preterm infants born before 30 weeks' gestation and less than two weeks old when extubated on to n-BiPAP will have a lower risk of extubation failure than infants extubated onto n-CPAP at equivalent mean airway pressure (MAP).

Methods

We conducted an unblinded multi-centre randomized trial comparing n-CPAP with n-BiPAP in babies born <30 weeks' gestation and < 2 weeks old. The primary outcome variable was the rate of extubation failure within 48 hours following the first attempt at extubation. Block randomization stratified by centre and gestation (< 28 weeks or ≥ 28 weeks) was performed.

Results

540 babies (270 in each group) were eligible to be included in the statistical analysis. 57 (21%) of n-BiPAP group and 55 (20%) of n-CPAP group failed extubation at 48 hours post-extubation (adjusted odds ratio: 1.01; 95% CI: 0.65 to1.56; p=0.97). Sub-group analysis of babies born before and after 28 weeks' gestation showed no significant differences between the two groups. There were no significant differences between arms in death; oxygen requirement at 28 days; oxygen requirement at 36 weeks' corrected gestation; intraventricular hemorrhage, necrotising enterocolitis requiring surgery or pneumothorax.

Conclusion

This trial shows that there is no added benefit to using n-BIPAP over n-CPAP at equivalent MAP in preventing extubation failures in babies born before 30 weeks' gestation and less than two weeks old.

INTRODUCTION

Babies born prematurely before 30 weeks' gestation are more likely to require ventilator support in the immediate neonatal period due to lung immaturity. Nasal continuous positive airway pressure (n-CPAP) has been shown to reduce the risk of extubation failure in this group of infants (1). In recent years, nasal biphasic positive airway pressure (n-BiPAP) has been introduced as an alternative to conventional n-CPAP but clear evidence of its benefit for immediate support following primary extubation compared with n-CPAP is so far lacking. In this study, we aimed to determine if the use of n-BiPAP is more effective than single level variable flow n-CPAP in preventing extubation failure when delivered at equivalent mean airway pressure (MAP) in babies born before 30 weeks' gestation.

PATIENTS AND METHODS

An unblinded multi-centre randomized trial of n-BIPAP vs. n-CPAP in infants born before 30 weeks' gestation and less than two weeks old was performed with an allocation ratio of 1:1. The trial protocol has been described in greater detail elsewhere [2]. No changes to trial protocol occurred following trial commencement. Our specific objective was to conduct a randomized controlled trial in infants born before 30 weeks' gestation and less than two weeks old to compare the risk of extubation failure over 48 hours after the first attempt at extubation to either n-BiPAP or n-CPAP at equivalent mean airway pressure (MAP).

Participants

The study was conducted in the north-west of England and was approved by North West 11 Research Ethics Committee. Eight regional neonatal intensive care units participated in the study.

Infants born before 30 weeks' gestation and less than two weeks old were eligible to participate in the study at the time of first extubation attempt following informed parental consent. Parents were approached from soon after birth and well in advance of an extubation attempt. Infants with major congenital malformations, upper respiratory tract abnormalities and neuromuscular disease were excluded. Infants known to have significant cranial ultrasound scan abnormalities (intraventricular hemorrhage with ventricular dilatation and/or parenchymal extension or white matter abnormalities) prior to extubation and those likely to be within 7 days post-laparotomy at the time of extubation were also excluded.

Interventions and treatment strategies

To be eligible for the first extubation attempt, the infant needed to be, (1) loaded with caffeine according to standard local protocol and have good respiratory effort persistently higher than the ventilator rate and (2) have satisfactory blood gases (defined as pH >7.25 and partial pressure of carbon dioxide <7 kPa (52.5 mmHg) on minimum ventilation (defined as MAP ≤7 cm water and fractional inspired oxygen concentration of ≤0.35). Unplanned extubation was included if the above criteria were satisfied within four hours prior to extubation and informed consent had been obtained.

The n-CPAP group received at extubation a single level continuous positive airway pressure of 6 cm water for at least 48 hours before weaning was commenced. If the infant was stable for the preceding 24 hours defined as having fewer than three minor apneas and no increase in oxygen requirement, weaning was permitted. Minor apnea was defined as apnea requiring stimulation but not mask ventilation. n-CPAP was decreased from 6 cm water by 1 cm water every 48 hours if

tolerated based on the above criteria. This was done until a pressure of 4 cm water was reached. If a pressure of 4 cm water was successfully tolerated for 48 hours then time off n-CPAP was allowed. Thereafter, no fixed weaning regime was prescribed.

The n-BiPAP group received at extubation a MAP of 6 cm water (baseline pressure of 4 cm water and peak pressure of 8 cm of water). Inspiratory time was set at one second and rate was set at 30/min. If the infant was stable for the preceding 48 hours at MAP of 6 cm water, weaning to MAP of 5 cm water (baseline pressure of 4 cm water and peak pressure of 6 cm of water) was permitted. If the infant was stable for the preceding 48 hours at MAP of 5 cm water, weaning to n-CPAP of 4 cm water was permitted. If the infant was stable for the preceding 48 hours at n-CPAP of 4 cm water, then time off n-CPAP was permitted. Thereafter, no fixed weaning regime was prescribed.

Routine hourly monitoring of heart rate, peripheral oxygen saturation and respiratory rate was performed as per standard care. Monitored oxygen saturations were maintained with the range 90 to 95% in all participating NICUs. Delivered n-CPAP and n-BiPAP pressures was monitored regularly and efforts were made to maintain desired n-CPAP and MAP levels in accordance with standard nursing practice. Active mouth closure with chin strap was not performed. Infants were followed up until death or discharge home from hospital. Surfactant was administered routinely for all ventilated infants soon after intubation.

Infants were determined to have a failed extubation attempt if there was, (1) uncompensated respiratory acidosis defined as pH <7.2 and partial pressure of carbon dioxide >8 kPa (60 mmHg) or (2) major apnea requiring mask ventilation during the first 7 days post-extubation. Cross-over

was not allowed when the criteria for failure of extubation were reached. Rescue treatment was provided by increasing pressures up to 6 cm of water if weaned or by re-intubation and ventilation.

Outcomes

Failure of extubation during the first 48 hours post-extubation was the primary outcome measure. Pre-specified secondary outcome measures were, (1) Maintenance of successful extubation for 7 days from the hour of extubation, (2) Number of ventilator days following first extubation attempt, (3) Oxygen requirement at 28 days of age and at 36 weeks' corrected gestation, (4) pH, partial pressure of carbon dioxide in the first post extubation gas done within two hours after extubation, (5) Duration of hospitalisation, (6) Rates of abdominal distension requiring cessation of feeds for 7 days post extubation, (7) Rate of apnea and bradycardia expressed as events per hour during the 48 hours following extubation and (8) Age at transfer back to referral centre in days.

Sample size

A sample size of 270 in each group was planned to give 80% power to detect a 10% reduction in the rates of extubation failure from 25% in the n-CPAP group to 15% in the n-BiPAP group at a 0.05 two-sided significance level. A 10% reduction in extubation failure rate was considered to be clinically significant and could support a change in practice to using n-BiPAP as first line treatment post-extubation.

Randomization

Infants were randomized following the decision to extubate using web-based randomization stratified by centre and gestation (<28 weeks or ≥28 weeks). The allocation sequence was computer-generated with blocks of random size between 2 and 8.

The participants were enrolled by the clinical team. The randomization was performed by the clinical team just prior to extubation. Intervention was commenced within four hours of the blood gas on which randomization was performed.

Blinding

The n-BiPAP device produces an audible noise which cannot be masked. Due to this, parents, clinicians involved in patient care and researchers assessing study end-points were not blinded to the nature of the study treatments.

Statistical methods

A formal statistical analysis plan was pre-specified. The primary efficacy analysis was conducted on an intention to treat basis. As the primary outcome variable is a binary (yes/no) outcome variable, groups were compared using a logistic regression model adjusting for the stratification variables. Effect sizes are summarised as odds-ratios with 95% CI and likelihood-ratio based significance levels computed.

The intention to treat (ITT) dataset comprised all correctly randomized patients based on trial inclusion and exclusion criteria. Sensitivity analyses were conducted using a per-protocol dataset (PP) which excluded all participants with major protocol breaches. Major protocol breaches were

those that occurred during the randomization process and within 48 hours following randomization and could potentially affect the primary outcome.

A subgroup analysis of the two gestation strata was pre-specified: an interaction term added to the model and a likelihood-ratio test was used to determine if there was any difference between the gestation groups and odds ratios presented for the two subgroups.

Secondary binary outcomes were analysed using the same approach and secondary numerical outcomes were analysed using similarly adjusted ordinary regression models. Time to event outcomes (days on ventilation and hospital stays) were log-transformed for analysis as log (time+1).

No interim analyses were planned or performed. Analyses were conducted in the R statistical environment v 3.1.0 [3].

Trial oversight

Data collection was performed by trained research staff on trial-specific case report forms and entered on a web based electronic case record form provided by OpenCDMS [4]. Safety monitoring was performed by Data Monitoring Committee.

Data processing was completed by screening for out-of-range data, with cross-checks for conflicting data within and between data collection forms by a data manager. A random 10% of

the data was independently validated against the source documents by the data manager and found to have no errors.

Safety monitoring was performed using a list of expected serious adverse events: (1) Intraventricular hemorrhage defined as hemorrhage causing ventricular dilatation with or without brain parenchymal involvement, (2) Periventricular leukomalacia on cranial ultrasound scan imaging, (3) Necrotising enterocolitis requiring surgery, (4) Patent ductus arteriosus (PDA) requiring treatment, (5) Retinopathy of prematurity requiring laser treatment, (6) Pneumothorax within 7 days after extubation, (7) Evidence of traumatic nasal injury, (8) Pulmonary hemorrhage and (9) Death.

RESULTS

544 infants were randomized between June 2011 and December 2014 from 8 neonatal intensive care units, with 270 in each arm in the ITT dataset after excluding 4 babies who were randomized in error. The median (range) number of patients recruited at each site was 69 (4-145). 304 were in the <28weeks' gestation strata and 236 were ≥28 weeks' gestation strata. All infants were ventilated after delivery, either according to clinical need due to respiratory distress syndrome (defined here as the early onset of respiratory distress requiring supplemental oxygen and respiratory support within four hours of delivery) or following intubation immediately after delivery for administration of surfactant. The participant flow was as shown in Figure 1. The commonest reason for major protocol breaches was partial pressure of carbon dioxide more than 7 kPa at the time of randomization. The commonest reason for loss to follow-up at 28 days and 36 weeks was death. Baseline characteristics were well balanced between the two groups as shown in

Table 1. The condition of infants prior to extubation was also comparable as shown in Table 2. The median (range) age of infants at extubation was 1 day (0-14).

Primary outcome

Extubation failed in 57/270 (21%) of the n-BIPAP group compared to 55/270 (20%) in the n-CPAP group, giving an odds-ratio of 1.01 (95% CI 0.65-1.56), P=0.97. Sensitivity analyses using the per-protocol dataset (PP) and gave very similar results with extubation failing in 50/259 (19%) of the n-BIPAP group compared to 52/254 (20%) of the n-CPAP group, giving an odds-ratio of 0.91 (95% CI 0.58-1.44), P=0.68.

Overall 91/304 (30%) extubations failed in the <28 weeks' gestation strata and 21/236 (9%) in the ≥28 weeks' gestation strata.

Secondary outcomes

The effect of treatment allocation on the secondary outcomes is shown in Table 3. There were no significant differences in any of the measures.

Adverse events

The effects of treatment allocation on the serious adverse events monitored were as shown in Table 4. 77 babies in the n-BiPAP group and 87 babies in the n-CPAP group had serious adverse events.

Sub-group analyses

There was no significant difference in the treatment effect (odds of extubation failure rate of n-BIPAP compared to n-CPAP) between the two gestation strata (P=0.997, interaction test). In the <28 weeks' gestation strata 47/157 (30%) of the n-BIPAP group compared to 44/147 (30%) in the n-CPAP group failed extubation, giving an odds-ratio of 1.01 (95% CI 0.61-1.67), P=0.97. In the ≥28 weeks' gestation strata 10/113 (9%) of the n-BIPAP group compared to 11/123 (9%) in the n-CPAP group failed extubation, giving an odds-ratio of 1.01 (95% CI 0.41-2.5), P=0.99.

DISCUSSION

In this large multi-centre randomized trial comparing n-BiPAP and n-CPAP at equivalent MAP in babies born before 30 weeks' gestation and less than two weeks old, we found no significant differences in extubation failure rates at 48 hours post-extubation between the two groups. There were no significant differences in the secondary outcomes including extubation failure at 7 days, oxygen requirement at 28 days and at 36 weeks' corrected gestation. There were also no significant differences in the duration of hospitalisation (total and post-extubation) and any of the serious adverse event outcomes monitored. The 95% CI of the almost zero effect of treatment translates to an absolute difference in extubation failure rates of (-5 to 7)%, less than the clinically relevant effect size specified before the trial began (±10%).

A limitation of the trial is the lack of blinding leaving a potential for bias. However, strict criteria for extubation failure were defined and monitored. Per protocol analyses excluding data when protocol deviations occurred showed no difference in results. As failure of extubation was based on blood gas criteria rather than response of the clinician to the blood gas parameters it was possible to be precise at the time at which the infant failed extubation attempt. Secondly, there is

no overall consensus on the optimal weaning strategy from CPAP. Our weaning protocol was based on consensus that it makes physiological sense to wean the mean airway pressure initially until the infant is stable on 4 cm water pressure as this avoids abrupt withdrawal of positive pressure and risk of atelectasis. Lastly, since we aimed to compare equivalent mean airway pressures in both arms, it can be argued that the baseline pressure during biphasic support was lower than the continuous distending pressure given in the corresponding CPAP arm. However, the baseline pressure was maintained at or above 4 cm water and is unlikely to have given rise to atelectasis or contributed any disadvantage to the n-BiPAP arm.

There have been few published trials to date directly comparing n-BiPAP with n-CPAP in preterm infants. Migliori et al. (2005) performed an unblinded crossover study comparing four alternating phases of n-CPAP and n-BiPAP in twenty infants (gestational ages 24 to 31 weeks) within 6 hours of weaning from mechanical ventilation [5] but delivered MAP was higher with n-BiPAP. Significant improvements in oxygen saturations and transcutaneous partial pressure of oxygen and carbon dioxide were noted during the n-BiPAP phases. There was also a significant reduction in spontaneous respiratory rate during the n-BiPAP phases. O'Brien et al. (2012) reported a randomized trial comparing n-BiPAP with n-CPAP following extubation in 136 infants with less than 1250 g birth weight using a similar design to the present trial. This also showed no apparent benefit between n-CPAP and biphasic pressure for support post extubation [6]. Lista et al. (2010) conducted a randomized controlled trial of 40 babies comparing the use of n-BiPAP with n-CPAP in premature infants following Intubation-Surfactant-Extubation (InSurE) approach [7]. They showed a significant reduction in duration of respiratory support, duration of oxygen dependency and gestational age at discharge in the group receiving n-BiPAP and no rise in inflammatory

cytokines as markers for associated lung injury, concluding that n-BiPAP was safe and well tolerated in this population. Kirpalani et al. (2013), conducted a randomized trial involving 1009 infants below 30 weeks' gestation and 1000g birth weight comparing different methods of non-invasive ventilation (defined as any technique combining n-CPAP with intermittent increases in applied pressure, including but not restricted to n-BiPAP) with n-CPAP and showed no difference in the rate of chronic lung disease or the need for intubation between the two groups. However, data related specifically to the efficacy of n-BiPAP in preventing chronic lung disease or extubation failure were not available [8]. More recently, Salvo et al. (2015) reported a randomized trial of synchronized nasal intermittent positive pressure ventilation (NIPPV) versus n-BiPAP for primary respiratory support in 124 infants less than 1500 g birth weight and less than 32 weeks' gestation which showed no difference in the requirement for intubation, death or broncopulmonary dysplasia between the two groups [9].

This trial for the first time clearly demonstrates that n-BiPAP confers no significant advantage on preventing primary extubation failure within the first 14 days of life when compared with n-CPAP at equivalent MAP (≤6 cm water) in infants born prior to 30 weeks' gestation. The results of this trial need to be applied cautiously in the broader neonatal population and beyond 14 days of age. At a later stage in neonatal care where there may be established parenchymal lung disease/ evolving chronic lung disease of prematurity, lung mechanics are different with poor compliance and non-homogeneous lung inflation. These infants are likely to require higher MAP and may also be at risk of uneven lung inflation with focal atelectasis along with areas of over-distension if continuous high MAPs are applied. It is possible that n-BiPAP could allow the delivery of MAP

(>6 cm water) with less risk of focal over-distension compared with n-CPAP at an equivalent MAP and further trials comparing n-BiPAP with n-CPAP in this population are warranted.

In the present trial, n-CPAP and n-BiPAP were delivered using the Infant Flow Advance (CareFusion–BD Inc.). This is a CPAP driver which has settings for single level or biphasic support via a distal interface comprising either nasal prongs or a nasal mask, both of which are sized appropriately for the individual infant and give consistent pressure delivery. Variable flow is generated by diversion of the inspiratory gases by the infant's expiratory flow at the distal interface (Fluidic Flip ^{TM}). n-CPAP is most commonly delivered using a variable flow device and we believe our findings are likely to be directly relevant to current neonatal practice using a comparable device for delivery of n-CPAP.

CONCLUSION

This trial provides clear and conclusive evidence that there is no clinically significant difference in extubation failure rates at 48 hours post extubation between n-BiPAP and n-CPAP at equivalent MAP when used in preterm babies born before 30 weeks' gestation and less than two weeks old.

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Trial Steering Committee (Independent members): JD Grainger, L Webster, S Rickard, L Livingstone
Data Monitoring Committee members: S Sinha, S Gupta, S Cotterill
Research Parent Group at St Mary's Hospital, Manchester
Sponsor: Central Manchester University Hospitals NHS Foundation Trust
Research Network: Clinical Research Network for Children, Manchester

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Figure 1: Participant flow chart

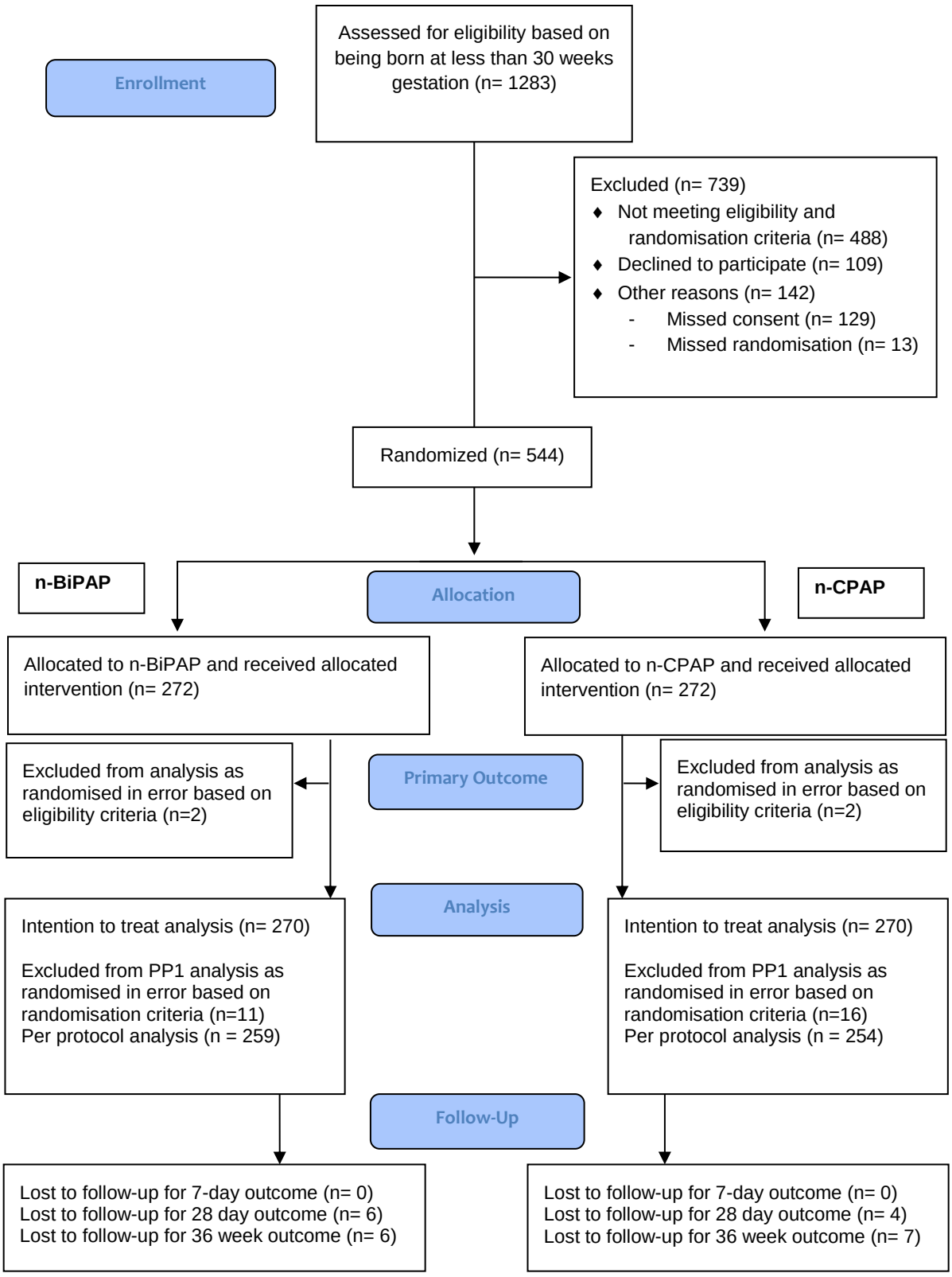
Enrollment
Assessed for eligibility based on being born at less than 30 weeks gestation (n= 1283)
Excluded (n= 739)
♦ Not meeting eligibility and randomisation criteria (n= 488)
♦ Declined to participate (n= 109)
♦ Other reasons (n= 142)
- Missed consent (n= 129)
- Missed randomisation (n= 13)
Randomized (n= 544)
n-BiPAP
Allocation
n-CPAP
Allocated to n-BiPAP and received allocated intervention (n= 272)
Allocated to n-CPAP and received allocated intervention (n= 272)
Excluded from analysis as randomised in error based on eligibility criteria (n=2)
Primary Outcome
Excluded from analysis as randomised in error based on eligibility criteria (n=2)
Analysis
Intention to treat analysis (n= 270)
Excluded from PP1 analysis as randomised in error based on randomisation criteria (n=11)
Per protocol analysis (n = 259)
Intention to treat analysis (n= 270)
Excluded from PP1 analysis as randomised in error based on randomisation criteria (n=16)
Per protocol analysis (n = 254)
Follow-Up
Lost to follow-up for 7-day outcome (n= 0)
Lost to follow-up for 28 day outcome (n= 6)
Lost to follow-up for 36 week outcome (n= 6)
Lost to follow-up for 7-day outcome (n= 0)
Lost to follow-up for 28 day outcome (n= 4)
Lost to follow-up for 36 week outcome (n= 7)

Table 1: Baseline characteristics of ITT dataset

			<28w n-BIPAP n=157	**<28W n-CPAP n=147**	**>28w n-BIPAP n=113**	**>28w n-CPAP n=123**
DEMOGRAPHICS						
Gender:	Male	N (%)	79 (50%)	75 (51%)	70 (62%)	57 (46%)
	Female	N (%)	78 (50%)	72 (49%)	43 (38%)	66 (54%)
Gestation age at birth (w)		Median (IQR)	26 (25-27)	26 (25-27)	29 (28-29)	28 (28-29)
Birth Weight g)		Median (IQR)	870 (750-985)	910 (791-1019)	1185 (1038-1335)	1173 (1022-1344)
Mother Age (y)		Median (IQR)	30 (25-34) [1]	29 (25-34)	28 (25-33)	29 (25-34) [2]
Mother's Ethnicity:	White	N (%)	116 (74%) [1]	108 (74%) [2]	88 (79%) [1]	95 (78%) [1]
	Asian	N (%)	26 (17%) [1]	17 (12%) [2]	16 (14%) [1]	20 (16%) [1]
	Black	N (%)	11 (7%) [1]	17 (12%) [2]	6 (5%) [1]	6 (5%) [1]
	Mixed/Other	N (%)	3 (2%) [1]	3 (2%) [2]	2 (2%) [1]	1 (1%) [1]
PERINATAL MANAGEMENT						
Delivery Type:	Vaginal Birth	N (%)	86 (55%) [1]	88 (60%)	39 (35%)	46 (37%)
	Elective CS	N (%)	8 (5%) [1]	11 (7%)	17 (15%)	11 (9%)
	Emergency CS	N (%)	62 (40%) [1]	48 (33%)	57 (50%)	66 (54%)
Antenatal Steroids: Yes*		N (%)	118 (77%) [3]	104 (72%) [3]	81 (74%) [3]	85 (71%) [3]
Surfactant given: Yes		N (%)	156 (100%) [1]	147 (100%)	113 (100%)	123 (100%)
Surfactant Doses		Median (IQR)	1 (1-2) [1]	1 (1-2)	1 (1-1) [1]	1 (1-2)
Surfactant Doses:	1	N (%)	114 (73%) [1]	108 (73%)	86 (77%) [1]	88 (72%)
	2	N (%)	35 (22%) [1]	35 (24%)	24 (21%) [1]	30 (24%)
	3	N (%)	7 (4%) [1]	4 (3%)	1 (1%) [1]	5 (4%)
	4	N (%)	0 (0%) [1]	0 (0%)	1 (1%) [1]	0 (0%)

Data in [ ] indicate number of missing data points; *Completed full course

Table 2: Condition of infants prior to first attempt at extubation

			<28w n-BIPAP n=157	<28W n-CPAP n=147	>28w n-BIPAP n=113	>28w n-CPAP n=123
RESPIRATORY STATUS DURING FIRST 12 HOURS AFTER BIRTH						
Max Base Deficit: (77%)	less than 7	N (%)	97 (62%)	95 (65%)	89 (79%)	95
	7 to 9.9	N (%)	38 (24%)	27 (18%)	16 (14%)	14 (11%)
	10 to 14.9	N (%)	19 (12%)	22 (15%)	7 (6%)	12 (10%)
	15 or more	N (%)	3 (2%)	3 (2%)	1 (1%)	2 (2%)
Min O_2: (98%) [1]	40% or less	N (%)	153 (98%) [1]	145 (99%) [1]	111 (98%)	120
	41% - 60%	N (%)	3 (2%) [1]	1 (1%) [1]	2 (2%)	2 (2%) [1]
	61% - 90%	N (%)	0 (0%) [1]	0 (0%) [1]	0 (0%)	0 (0%) [1]
	91% - 100%	N (%)	0 (0%) [1]	0 (0%) [1]	0 (0%)	0 (0%) [1]
Max O_2: (74%) [1]	40% or less	N (%)	120 (77%) [2]	102 (71%) [4]	90 (80%)	90
	41% to 60%	N (%)	23 (15%) [2]	28 (20%) [4]	15 (13%)	24 (20%) [1]
	61% to 90%	N (%)	5 (3%) [2]	9 (6%) [4]	3 (3%)	5 (4%) [1]
	91% to 100%	N (%)	7 (5%) [2]	4 (3%) [4]	5 (4%)	3 (2%) [1]
VENTILATORY STATUS PRIOR TO EXTUBATION						
Ventilator Days		Median (IQR)	2 (1-3) [1]	2 (1-3) [1]	1 (1-2)	1 (1-2)
Peak inspiratory pressure		Median (IQR)	16 (14-16) [1]	16 (14-16)	16 (14-16) [1]	16 (15-17)
PEEP		Median (IQR)	4 (4-5) [1]	4 (4-5)	4 (4-5) [1]	4 (4-5)

Mean airway pressure (5.6-6.6)	Median (IQR)	6.1 (5.6-6.6)	6.3 (5.4-6.8)	6.1 (5.7-6.6)	6.1
Ventilator rate 30)	Median (IQR)	25 (20-30) [1]	25 (20-30)	25 (20-30) [1]	25 (20-
Inspiratory time (s) (0.35-0.40)	Median (IQR)	0.36 (0.35-0.40) [1]	0.35 (0.34-0.40)	0.36 (0.35-0.40) [1]	0.38
Oxygen requirement (%) 22)	Median (IQR)	21 (21-24)	21 (21-23)	21 (21-21)	21 (21-
VITAL SIGNS PRIOR TO EXTUBATION					
Respiratory rate 70) [4]	Median (IQR)	59 (45-66) [5]	58 (45-65) [4]	60 (46-70) [3]	60 (50-
Heart rate (135-155) [2]	Median (IQR)	150 (140-160) [3]	153 (142-162)	145 (136-152) [1]	145
Oxygen saturation (%) 99) [4]	Median (IQR)	96 (94-98) [2]	95 (94-97)	97 (95-98) [1]	96 (94-
Body temperature (°C) (36.8-37.2) [5]	Median (IQR)	37.0 (36.8-37.2) [6]	37.0 (36.8-37.3 [2]	37.0 (37.0-37.3) [4]	37.0
BLOOD GAS PARAMETERS PRIOR TO EXTUBATION					
pH (7.3-7.4)	Median (IQR)	7.4 (7.3-7.4)	7.3 (7.3-7.4)	7.4 (7.3-7.4)	7.4
PCO_2 (4.3-5.6)	Median (IQR)	5.0 (4.3-5.7)	5.0 (4.5-5.9)	5.0 (4.3-5.7)	4.9
Base Excess 5-2) [2]	Median (IQR)	-4.2 (-5.9-2.6) [5]	-3.8 (-5.3-2.1) [6]	-2.9 (-5-0.8) [2]	-3.6 (-
Bicarbonate (mEq/L) 23) [3]	Median (IQR)	21 (19-22) [1]	21 (20-22) [2]	22 (20-24) [3]	21 (20-

Data in [ ] indicate number of missing data points; O_2: oxygen; PCO_2: Partial pressure of blood carbon dioxide; PEEP: Positive end expiratory pressure

Table 3: Secondary outcomes

		Outcome in each arm		Treatment effect		
		n-BIPAP	**n-CPAP**	**Measure**	**Effect**	**P**
Extubation failure at 7 days	N (%)	92 (34%)	85 (31%)	Odds Ratio	1.10 (0.74 to 1.62)	0.65
Ventilator days post extubation	Mean (SD) †	1.9 (3.6) [5]	2.2 (3.8) [1]	Diff in log	-0.15 (-0.35 to 0.04)	0.13
Days on non-invasive ventilation	Mean (SD) †	24.1 (23.7) [6]	23.9 (22.4) [5]	Diff in log	-0.01 (-0.16 to 0.14)	0.884
Oxygen requirement at 28 days	N (%)	190 (72%) [6]	191 (72%) [4]	Odds Ratio	0.96 (0.63 to 1.45)	0.84
Oxygen requirement at 36 w	N (%)	132 (50%) [6]	143 (54%) [7]	Odds Ratio	0.78 (0.54 to 1.13)	0.18
pH (post-extubation blood gas)	Mean (SD)	7.34 (0.07) [8]	7.35 (0.07) [6]	Difference	0.00 (-0.01 to 0.01)	0.61
$PaCO_2$ (post-extubation blood gas)	Mean (SD)	5.33 (1.19) [10]	5.3 (1.18) [7]	Difference	0.01 (-0.18 to 0.21)	0.89
Duration of hospitalisation (days)	Mean (SD) †	75.3 (25.2) [18]**	76.7 (26.3) [16]**	Diff in log	-0.03 (-0.08 to 0.02)	0.18
Abdominal distension*	N (%)	9 (3%)	6 (2%)	Odds Ratio	1.50 (0.52 to 4.31)	0.45
Apnoea and bradycardia#	N (%)	63 (23%)	57 (21%)	Odds Ratio	1.09 (0.71 to 1.68)	0.68
Age at transfer back to referral center (days)	Mean (SD) †	23.6 (22.0) (n= 110)	21.3 (23.1) (n=103)	Diff in log	0.08 (-0.15 to 0.32)	0.49

Data in [ ] indicate number of missing data points; *requiring cessation of feeds during 7 days post extubation; #major apnoea requiring mask ventilation or intubation during 7 days post extubation; **data missing due to deaths, † Mean computed on log-scale and back-transformed

Table 4: Serious adverse events in each trial arm. P is significance level from a Fisher's Exact test.

	n-BIPAP	**n-CPAP**	**P**
Death	18	17	0.86
Necrotisong enterocolitis requiring surgery	9	10	1
Pulmonary haemorrhage	5	9	0.42
Retinopathy of prematurity requiring treatment	4	4	1
PDA requiring medical treatment	23	24	1
PDA requiring surgery	2	4	0.69
Cystic periventricular leukomalcia on cranial ultrasound	8	8	1
Intraventricular haemorrhage* on cranial ultrasound	13	13	1
Pneumothorax	9	5	0.29
Traumatic nasal injury	4	10	0.17

* causing ventricular dilatation or brain parenchymal involvement;