Extending CPAP Therapy in Stable Preterm Infants to Increase Lung Growth and Function: A Randomized Controlled Trial

The eCPAP STUDY

Statistical Analysis Plan (SAP)
Version 1: August 20, 2023

Version Date	Version	
August 20, 2023	1	Initial release

Specific Aims:

We hypothesize that extended CPAP (eCPAP) in stable preterm infants in the neonatal intensive care unit (NICU) will increase alveolar volume (V_A), lung diffusion capacity (DLCO), and forced expiratory flows (FEFs) measured at approximately 6 months corrected age compared to stable preterm infants who had CPAP discontinued by clinical criteria. Infants stratified by gestational age will be allocated to CPAP discontinuation (dCPAP, usual care) or eCPAP for 2-weeks to address the following Specific Aims:

Specific Aim 1 / Primary Outcome:

Establish that 2 additional weeks of CPAP in the NICU for stable preterm infants increases alveolar volume at approximately 6 months of corrected age compared to infants who have CPAP discontinued, usual care.

Specific Aim 2 / Secondary Outcomes:

Establish that 2 extra weeks of CPAP in stable preterm infants increases DLCO and FEFs at approximately 6 months of corrected age versus infants who have CPAP discontinued, usual care.

Specific Aim 3 / Exploratory Outcomes:

Evaluate whether 2 extra weeks of CPAP in stable preterm infants results in lower respiratory morbidity and/or improved neurodevelopmental outcomes through 12 months of corrected age compared to infants who had CPAP discontinued, usual care. This will provide pilot data for a future multi-center randomized trial.

Population:

Screened:	All infants delivered at OHSU at ≤ 32 and 6/7 weeks gestation and who required CPAP for ≥ 24 hours.
Screen Failed:	Met any exclusion criteria.
Enrolled:	All infants consented into study.
Intention-to-treat (ITT):	All enrolled infants who met eCPAP stability criteria prior to 35 weeks of postmenstrual age/ corrected gestational age and were randomized or assigned[1] to a treatment group will be analyzed in that group.
Per protocol:	Only randomized or assigned infants[1] who received the treatment intervention as allocated will be included, that is who received the allocated treatment intervention for ≥ 9 days of the 14 day treatment period
As treated:	All randomized or assigned infants will be analyzed based on the treatment actually received regardless of the allocation assignment.
Completed:	All randomized or assigned infants who had not discontinued and had not been withdrawn.
Discontinued:	All randomized or assigned infants who were withdrawn by investigator.
Alveolar volume completed:	Have a completed procedure with a corrected age of approximately 6 months (allowable range of 4 – 12 months corrected age).

DLCO completed: Have a completed procedure with a corrected age of approximately 6 months (allowable range of 4 – 12 months corrected age).

FEFs completed: Have a completed procedure with a corrected age of approximately 6 months (allowable range of 4 – 14 months corrected age).

Clinical Respiratory Outcome Done: Have at least one respiratory questionnaire completed at 4 months of corrected age or later.

Neurodevelopmental Outcome Done: Have a neurodevelopmental exam completed at less than or equal to 16 months of corrected age.

[1] 2nd twin is assigned to same arm as 1st twin that is randomized

Data Analyses:

1) Outcomes data will initially be analyzed by ITT, according to the treatment arm the infants were randomized or assigned to, regardless of treatment adherence. **THIS IS THE PRIMARY ANALYSIS**.
2) Outcomes data will secondarily be analyzed by per protocol analyses, that is only the infants who received the intervention as randomized or assigned will be included.
3) Outcomes data will be analyzed by "as treated analyses" by the treatment received.

POWER AND STATISTICAL CONSIDERATIONS/ANALYSIS

Statistical Analysis. All outcomes will be analyzed by a statistician blinded to the infants' treatment assignments by intention to treat. Maternal and infant characteristics will be compared using the independent-samples t-test for continuous measures (or the Wilcoxon–Mann–Whitney test for nonnormal distributions) and the chi-square test for categorical variables. We will examine the distributions of continuous variables and use alternative approaches such as transformation or nonparametric methods in cases of violation to the normal distribution assumption. We will examine the frequency distribution of all categorical variables and adopt exact inference procedures in cases of zero or small cell size. All analyses will be conducted using the SAS 9.4 (SAS Institute, Carey, NC).

Specific Aim 1 (Primary Outcome): General linear mixed models (GLMMs) models will be used to compare the primary outcome of alveolar volume (V_A) between the eCPAP and CPAP discontinuation group while adjusting for gestational age at delivery (randomization stratification variable) and other baseline variables that are found to be statistically different between the two groups. Since the lung function measures are highly dependent on infant length and sex, we will further adjust for length and sex in the GLMMs as indicated. In order to adjust for intra-twin correlations, generalized estimating equations (GEEs) with the linear link function will be used to model V_A. The GLMMs can be performed using the GEE estimation approach. Intention to treat analysis will be used for the primary analysis of all aims.

Specific Aim 2 (Secondary Outcomes): Lung diffusion capacity (DLCO) and forced expiratory flows (FEFs) and specifically FEF_{50} will be analyzed with the same general approaches described for the primary outcome of V_A in Specific Aim 1.

FRC measurements in the NICU done pre and post randomization and FEF_{25-75}, FEF_{75} done at 6 months of corrected age will be analyzed with the same general approaches as above in Specific Aim 1.

Specific Aim 3 (Exploratory Outcomes): Logistic regression models will be used to compare the incidence of wheeze and the incidence of wheeze and cough between the two groups adjusting for gestational age at delivery (See appendix for standardized respiratory questionnaire administered). Neurodevelopmental scores will be analyzed with the same general approaches described for the primary outcome of V_A in Specific Aim 1.

Intention to treat analysis will be used for the primary analysis of all aims. In addition, all of the aims will also be analyzed with the same general approach using a per protocol analysis and "as treated analysis".

Sample Size and Power Considerations. No studies have compared V_A at 6 months of age in stable infants randomized to eCPAP versus CPAP discontinuation in the NICU. Data from our pilot eCPAP study showed a 12% higher FRC in infants randomized to eCPAP at the end of two week treatment period[1]. A study by Dr. Tepper et al reported a 16% difference in both V_A and D_L in preterm infants according to CPAP treatment in the NICU (Table 1)[2] and a 12% difference in D_L between infants with BPD versus healthy term infants[3]. Therefore, we powered our randomized trial to detect a 12% difference in V_A between the eCPAP and CPAP discontinuation groups.

Table 1. Estimated power for 34 infants per group with completed PFT data

Outcome Measures	Mean (SD) in Control Group	Estimated Power for Group Differences		
		12%	15%	17%
Alveolar volume (V_A)	642 (189)	80	92	97
Lung diffusing capacity (D_L)	4.1 (1.19)	80	92	98
Forced Expiratory Flow (FEF_{50})	346 (129)	35	49	60

Using ANCOVA model and assuming a mean V_A of 642 mL (SD=189) based on data of the overall mean and SD from the control and CPAP groups reported in Assaf et al[2], a sample size of 34 infants per group is needed to yield 80% power for detecting a 12% difference (effect size=0.42) in V_A in the eCPAP group at α=0.05. This sample size also allows us to detect a 12% difference in D_L with an effect size of 0.42. We estimate that 18% of the study patients will be twin pairs based on our pilot eCPAP study. Conservatively counting just one infant out of each twin pair for sample size estimation, we will need 38 infants per group (76 total infants at 6 months) with completed V_A outcomes. We further assume a 10% missing data in the NICU (unsuccessful test or infants transferred to another facility) and a 15% loss from NICU discharge to the 6 month PFT (cohort loss, unacceptable PFT, unsuccessful sedation) and therefore we will need to randomize and/or assign 50 infants per group (total n=100) into the trial. This sample size will provide 80% power for detecting an effect size difference of 0.42 in outcome measures between the two groups in Aim 1 (primary outcome of V_A) and Aim 2 for D_L. This sample size allows us to detect a 23% difference in FEF_{50}.
With regards to the exploratory clinical respiratory outcome, published data in 48 preterm infants with average GA of 28 weeks who did not develop BPD (similar to the group we project to recruit) reported a 48% incidence of wheeze in the first year of life[4]. These researchers also documented a 21% incidence of wheeze in 195 term infants. In our initial vitamin C study[5] using the same questionnaire we will use in this proposed eCPAP study, 76 term infants born to non-smokers had a 27% incidence of wheeze in the first year of life. Based on these data, we project that 48% of the infants who have CPAP discontinued by the CPAP stability criteria will have wheeze in the first year of life. With our projected sample size of 50 per group accounting for a 15% missing questionnaire rate, we will have 70% power to show a decrease in the incidence of wheeze from 48% to 21%, and 90% power to show a decrease in wheeze and cough from 79% to 50%.

Interim analysis and stopping rules. No interim analysis for efficacy is planned. There will be no pre-specified stopping rules, but the DSMB will review SAEs as they occur. Although this is a fragile population, based on our pilot eCPAP study, the fact that infants will be convalescing by the time they are enrolled in the study, and our experience with sedation in the VCSIP, we do not anticipate a large number of SAEs but will be vigilantly monitoring. The DSMB chair may call a DSMB meeting to specifically review safety concerns.

References:

1.Lam R, Schilling D, Scottoline B, Platteau A, Niederhausen M, Lund KC, Schelonka RL, MacDonald KD, McEvoy CT. The effect of extended continuous positive airway pressure on changes in lung volumes in stable premature infants: A randomized controlled trial. J Pediatr 2020; 217: 66-72.e.1.

2.Assaf SJ, Chang DV, Tiller CJ et al. Lung parenchymal development in premature infants without bronchopulmonary dysplasia. Pediatr Pulmonol 2015;50:1313-1319.

3.Balinotti JE, Chakr VC, Tiller C et al. Growth of lung parenchyma in infants and toddlers with chronic lung disease of infancy. Am J Respir Crit Care Med 2010;181:1093-1097.

4.Pramana IA, Latzin P, Schlapbach LJ et al. Respiratory symptoms in preterm infants: burden of disease in the first year of life. Eur J Med Res 2011;16:223-230.

5. McEvoy CT, Schilling D, Clay N, Jackson K, Go MD, Spitale P, Bunten C, Leiva M, Gonzales D, Hollister-Smith J, Durand M, Frei B, Buist AS, Peters D, Morris CD, Spindel ER. Vitamin C supplementation for pregnant smoking women and pulmonary function in their newborn infants: a randomized clinical trial. JAMA. 2014; 311(20): 2074-82.

Appendix: Clinical Respiratory Outcome

The wheeze outcome quantified between the infant's discharge from the Neonatal Intensive Care Unit through 12 months of age was obtained from the following specific questions contained on the standardized respiratory questionnaire[1,2] which was administered monthly to the child's primary caretaker. A positive response to any of these questions on one or more respiratory questionnaire was recorded as a positive for the wheeze outcome. (The numbers below refer to the question number on the respiratory questionnaire and are organized by source: parental report; healthcare provider; medication use)

Field Label	Response Required/ Composite Notes (which to count)
PARENTAL REPORT	
1. Since [birth/the last time we talked] has your child had wheezing or whistling in his/her chest?	Any yes, ever. Include an overall count of individuals that answered yes as well as a second count of individuals that reported yes 2 or more times
14. Has child had any of the following illnesses?	14c. Bronchitis=1 (Yes) 14d. Bronchiolitis=1 (Yes)
HEALTHCARE PROVIDER	
2. Since [birth/the last time we talked] has a health care provider said that your child has wheezy or asthmatic bronchitis?	Response = 1 (Yes)
3. Since [birth/the last time we talked] has a health care provider said that your child has asthma?	Response = 1 (Yes)
18. Reason for hospitalization code	Response = 3 (Bronchitis) or 4 (Bronchiolitis) or 5 (Wheezing) or 8 (Asthma/asthma exacerbation)
19. Not counting hospitalizations, has [CHILD] been seen by a doctor or health care provider because of problems with wheezing, asthma, or wheezy or asthmatic bronchitis, since [birth/the last time we talked]? Include visits to an emergency room, a doctor's office, urgent care, or clinic.	Response = 1 (Yes)
MEDICATION USE	
4a. Since the last time we talked, OR in the last 12 months, which of the following types of medication has child been given?	4a1. Bronchodilator inhalers/nebulizers, pills, or syrups= 1 (Yes) 4a2. Steroid inhalers/nebulizers= 1 (Yes) 4a3. Leukotriene modifiers=1 (Yes) 4a4. Steroid pills or liquids= 1 (Yes) 4a6a. If other, specify medication types. Refer to wheeze_med___1=1 (Checked)
10b. Has child been given any medicine for a cough when he/she did not have a cold?	10b1a. Bronchodilator inhalers/nebulizers, pills, or syrups= 1 (Yes) 10b1b. Steroid inhalers/nebulizers= 1 (Yes)

Field Label	Response Required/ Composite Notes (which to count)
	10b1c. Leukotriene modifiers=1 (Yes) 10b1d. Steroid pills or liquids= 1 (Yes) 10b1f . If other, specify medication types. Refer to wheeze_med___1=1 (Checked)
17. Specify other medications [1]	refer to wheeze_med____1= 1 (Checked)
18c. Nebulizer/Inhaler (breathing) Treatment in Hospital?	Response = 1 (Yes)
If Other medication was used, medication was	Response = 1 (Yes)

[1] Other medications: albuterol, albuterol nebulizer, pills, or syrups, steroid inhalers, nebulizers, leukotriene modifiers, steroid pills or liquids

References:

1.Ferris BG. Epidemiology Standardization Project (American Thoracic Society). *Am Rev Respir Dis* 1978;118:1-120.

2.Litonjua AA, Carey VJ, Laranjo N et al. Effect of Prenatal Supplementation With Vitamin D on Asthma or Recurrent Wheezing in Offspring by Age 3 Years: The VDAART Randomized Clinical Trial. *JAMA* 2016;315(4):362-370.