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Comparison of Sprinting vs. Non-Sprinting to Wean Nasal Continuous Positive Airway Pressure Off in Very Preterm Infants

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Abstract

Objectives: Though Nasal Continuous Positive Airway Pressure (NCPAP) is commonly used for non-invasive neonatal respiratory support, the optimal method of weaning NCPAP is not established. In this prospective, two-center randomized control trial we hypothesize that gradually increasing spontaneous breathing time off NCPAP increases successful weaning from NCPAP in infants born <31 weeks gestational age.

Methods and Study Design: Infants were randomized to one of the two NCPAP weaning protocols, a sprinting, i.e., gradually increasing spontaneous breathing time off CPAP, protocol vs. a non-sprinting (weaning pressure down) protocol.

Results: Eighty-six infants were enrolled in one of the two study groups. Thirty-one infants (77%) in the sprinting group and 30 (75%) in the non-sprinting group were successfully weaned off NCPAP at the first attempt ($p > 0.05$)**.** It took 1.3 (1-1.75) (median (IQR)) attempts & 7 (7-7) days to wean NCPAP off in the sprinting group vs. 1.3 (1-1.75) attempts & 7 (7-10) days in the non-sprinting group ($p > 0.05$). Additionally, no differences in the secondary outcomes of bronchopulmonary dysplasia, severe retinopathy of prematurity (≥ stage 3), periventricular leukomalacia, and length of stay were noted between the two groups.

Conclusion: Weaning NCPAP via sprinting or non-sprinting protocol is comparable, not only for successful weaning, but also for the occurrence of common neonatal morbidities that impact the long-term outcome in premature infants. (ClinicalTrials.gov number, NCT02819050)

Introduction

Many studies [1-3] have demonstrated the benefits of Nasal Continuous Positive Airway Pressure (NCPAP) in managing infants with respiratory distress and apnea. A growing body of observational studies [4-8], clinical trials [1, 9-11], and reviews [12-15] suggest a role for the use of early CPAP as a means to decrease the need for mechanical ventilation without increasing morbidity. However, the optimal method of weaning off NCPAP is not established. Premature discontinuation of CPAP carries the risk of atelectasis and development of apneas and bradycardias, whereas unnecessary continuation exposes the infant to the potential side effects—gastric distension, nasal trauma, agitation, and long-term consequences of alveolar over distension.

In a meta-analysis on CPAP weaning methods, Jardine et al reviewed [16] Cochrane Neonatal Review Group, MEDLINE from 1966 to June 2010, CINAHL from 1982 to June 2010, and the Cochrane Central Register of Controlled Trials; the authors highlighted the need for more randomized controlled trials to address this important issue. In contrast, in their review, Amatya et al concluded that a successful wean tended to occur at 32-33 weeks corrected GA (CGA), at 1600g body weight, and the commonly used methods for weaning included sudden stoppage, a gradual pressure wean, and a gradual graded time off wean [17].

This study was designed to test the hypothesis that gradually increasing spontaneous breathing time off NCPAP, i.e., sprinting (SP), increases successful weaning off NCPAP in infants born at < 31 weeks GA.

Subjects and Methods

This prospective, two-center, randomized controlled trial was performed at Children's Hospital of Orange County and Harbor UCLA Medical Center NICUs from January 2014-January 2016. We compared a strategy of weaning NCPAP via SP versus non-sprinting (NSP) approach with the primary outcome assessed after 7 days on protocol and the secondary outcomes assessed prior to discharge, transfer or death. This study was approved by the Institutional Review Board at both hospitals. Informed consent was attained from at least one parent of each infant studied. Both institutions utilized bubble CPAP during the study period.

Infants included were born at 23 0/7-30 6/7 weeks gestation. On meeting the below outlined eligibility criteria, infants were randomized to wean via SP (See "sprinting off" protocol below) versus a NSP approach (See "Weaning pressure down" protocol below) in blocks of four at the each participating center. Duration of wean for each group was 72h. Randomization list was created online via electronic randomization plan generator at the website www.randomization.com. Babies were randomly assigned, unmasked, to a group as they enrolled.

Eligibility criteria

To be enrolled in the study, infants had to be born between 23 0/7-30 6/7 weeks GA, on NCPAP for at least 24h, meet the criteria defined in the "Stability criteria" section below and they had to be stable on ≤0.3 FiO_2 for at least 24h. Initiation of study protocol, i.e., weaning from NCPAP, was started when infant met all of the following additional criteria for at least 24h:

- At least 26 0/7 weeks CGA.

- NCPAP of 5-6 cm of H_2O.
- Loaded with caffeine (caffeine citrate 20 mg/kg) or already on maintenance (caffeine citrate 10 mg/kg/day).
- Stable respiratory system assessment [respiratory rate (RR) of < 70/min, no significant chest retractions, and baseline oxygen saturation > 86%] and otherwise deemed clinically stable to wean of NCPAP.
- If post-surgery, infant must be at least 2 weeks post-operative and off antibiotics with no concern for repeat surgery.
- A documented hemoglobin level of ≥ 8 g/dl within 7 days of the initiation of the study.

Exclusion criteria

Infants were excluded if there was evidence of a hemodynamically or clinically significant PDA diagnosed either clinically (with worsening respiratory status or pulmonary edema on chest x-ray) and/or echocardiographically; any significant congenital abnormality (abnormalities affecting a major organ system, airway, or musculoskeletal system); suspected or proven sepsis (positive blood culture); or grade IV intraventricular hemorrhage (IVH).

Stability criteria

The infant met stability criteria if it required a flow of ≤ 2 liters via nasal cannula (NC, delivering heated and humidified flow) and FiO_2 of ≤ 0.30 to keep SaO_2 levels above 86% without any documented apnea or bradycardia > 20s duration, and have a RR of < 70 for more than 24h without significant chest retractions.

Failure Criteria

The infant was deemed to have failed the intervention if infant developed increased work of breathing (intercostal recession and accessory muscle use) with RR > 70 for over 1h continuously AND FiO_2 of > 0.30 and/or > 2 liters via NC to keep SaO_2 levels over 86%, OR apnea or bradycardia requiring resuscitation, ranging from bag and mask ventilation to intubation.

Sprinting Protocol

Infants randomized to the SP group were slowly weaned off NCPAP per the following protocol,

- 3h off to no > 2 liters NC every 12h for first 24h. If met stability criteria then,
- 6h off to no > 2 liters NC every 12h for next 24h. If met stability criteria then,
- 9h off to no > 2 liters NC every 12h for next 24h. If met stability criteria then,
- Placed on NCPAP +5 for 24h for re-recruitment. If met stability criteria, then
- Switched to room air (no flow) or no > 2 liter flow via NC, i.e., the providers were given the discretion of being able to wean off NCPAP by switching to 0.5 liter NC and titrating as needed to keep FiO2 to less than 0.3. They also had the option of placing the infant directly on room air if clinically deemed acceptable.
- Of note, whenever the infant failed wean, at any step during the weaning process, infant was placed one-step back on the SP protocol for at least 24h before attempting the wean again.

Non-sprinting Group

Infants randomized to the NSP group were turned off NCPAP per the following protocol,

- If the infant was on NCPAP of +6 cm of H_2O
  - Infant was weaned down to CPAP 5 x 96h.
  - If infant met the stability criteria, then infant was switched to room air (no flow) or no > 2 liter flow via NC.
- If the infant was on NCPAP +5 cm of H_2O
  - The infant was continued on CPAP +5 cm of H_2O x 96h
- If infant met the stability criteria, then infant was switched to room air (no flow) or no > 2 liter flow via NC. For further weaning, the providers were given the same options as in the SP group.

In both groups, if the infant failed to meet stability criteria, patient was placed back on NCPAP for at least 24h, and when stability criteria met again, the infant was placed back on the previously tolerated setting on the weaning protocol.

Outcomes Measured

The primary outcome measured was the successful wean off NCPAP during the first trial, which was defined as a total of 7 days (4 days of weaning and 3 days of observation afterwards.) Infants meeting the primary outcome criteria must have completed the 7 days without meeting any of the failure criteria. Secondary outcomes measured included the number of attempts to wean off NCPAP; number of days on the weaning protocol before successful NCPAP wean; the incidence of BPD, severe retinopathy of prematurity (ROP, ≥ stage 3), periventricular leukomalacia (PVL), length of stay and CGA at time of discharge. BPD, ROP, and PVL were defined as per the CPQCC (California Perinatal Quality Care Collaborative) manual of definitions [18].

Statistical Analysis

Data were analyzed based on an intention-to-treat. We calculated that a total sample size of 80 (40 infants in each group) would provide 80% power to detect the difference of 30% between the two groups with a p value of ≤ 0.05, based on the historical 50% success rate in weaning off CPAP for the control group using a one-sided Chi-square test. For the binary outcomes, we utilized the Chi-square test if the data were comparable between the groups, or the Fisher's exact test if the data differed significantly between the two groups. For the continuous outcomes (i.e. duration off CPAP, length of hospital stay, etc.), we used the two sample t-test (two-tailed) if the data had a normal distribution and the Wilcoxon rank-sum test if the data distribution was not normal.

Results

One hundred and fifty-two infants were evaluated and 86 were enrolled. (Fifty-five did not meet eligibility criteria and 11 declined). Forty patients each were randomized to the SP and NSP group. Six patients were enrolled but not randomized (3 were withdrawn due to parental request, 2 were withdrawn due to neonatologist discretion and 1 was extubated directly to NC) (See Figure 1).

Clinical and demographic data for infants in the two groups are shown in Table 1. Infant birth weight, sex, GA at birth, CGA at study initiation, race, exposure to antenatal steroids, and diagnosis of clinical chorioamnionitis (defined based on maternal temperature, fundal tenderness, foul smelling amniotic fluid requiring prenatal antibiotic administration), PDA, and anemia did not differ statistically between the two study groups. Baseline CPAP level on average at the time of initiation of study was +5 cm of H_2O with $FiO_2 < 0.3$, indicating comparable underlying initial disease severity of respiratory illness between the groups.

Thirty one infants in the SP group versus 30 infants in the NSP were successfully weaned off NCPAP at first trial ($p > 0.05$). Number of attempts 1.3 (1-1.75) versus 1.33 (1-1.75) {median (IQR)} to wean off NCPAP and number of days on NCPAP protocol 7 (7-7) versus 7 (7-10) were also not statistically different between the two groups (Table 2). The other secondary outcomes (BPD, ROP, PVL, length of stay, and CGA at time of discharge or transfer) were also not significantly different between the groups (Table 3).

In analyzing center-specific data, at one institution (N=19), we found a statistically significant greater first attempt success ($p= 0.017$); fewer attempts to wean off NCPAP ($p=0.018$); and fewer days on study protocol ($p=0.05$) with the NSP approach. However, there were no statistically significant differences in other secondary outcomes between the groups. In the other

center (N=61), there was no statistically significant difference in the first attempt wean success, number of attempts to achieve successful wean, overall days on study protocol, or any other secondary outcome between the groups (p>0.05 for all).

Discussion

In a randomized controlled trial, we compared SP and NSP approaches to wean of NCPAP in infants born between 23 0/7-30 6/7 weeks GA. There was no statistically significant difference in successful weaning off NCPAP during the first trial via SP versus NSP approach.

Some studies [1,2,9] have demonstrated NCPAP to be a valid alternative to intubation and surfactant administration, which has led to its increased use in recent years. The optimal timing and method of weaning from NCPAP is not established. In a survey of Australian and New Zealand neonatologists, 56% stated that their approach to NCPAP weaning was "ad hoc" [16], rendering the present study highly relevant. Previous attempts to address the optimal NCPAP weaning strategy have been flawed due to significant methodological issues including but not limited to small sample size, selection bias, variations in patient populations studied, and the lack of details on the weaning protocols used in these studies.

Only a handful of previous studies [19-22] have addressed methods of weaning CPAP in neonates. Randomizing infants <1500g BW with adequate SaO2 levels on <0.3 FiO_2 and NCPAP to either gradual pressure reduction or increasing the duration of time off NCPAP, Singh el al [20] concluded that weaning pressure might lead to more rapid weaning than increasing the

time off NCPAP. However, there was a significant imbalance in the number of infants randomized to each study group. In another study, comparing weaning pressure versus time off NCPAP in 24-31 weeks GA infants, Soe [21] found that in infants over 28 weeks GA there was no difference in success between the two approaches, but in infants 24-27 weeks GA, pressure weaning proved to be more effective. Unfortunately, the timing to wean from NCPAP was neither standardized, nor accounted for in their analysis.

Our findings are similar to those of Rastogi et al who, in comparing sudden discontinuation versus gradual pressure weaning strategy found no difference in success between these two approaches for weaning from NCPAP [23]. That study, however, was a single center study, had a smaller sample size (56 infants), and included somewhat larger GA infants. In contrast, Todd et al demonstrated that sudden CPAP discontinuation group versus the SP group had a shorter CPAP weaning time, total duration on CPAP, need for oxygen supplementation, duration of hospitalization, along with a reduction in the incidence of BPD [22]. Follow-up studies [24,25] from this cohort demonstrate that utilizing the sudden wean off method reduces CPAP time, CGA to cease CPAP, PDA and BPD, without adversely affecting weight gain, and time to reach full feeds premature babies <30 weeks gestation. It is important to point out that no study that systematically examined the success rate of yet another popular method of weaning NCPAP, i.e., a gradual reduction in FiO_2, while maintaining CPAP at 5 cm of H_2O, has been published. However, it is anticipated that many infants not requiring supplemental oxygen while on CPAP might require it following CPAP discontinuation.

We acknowledge that due to logistic reasons this was a non-blinded study; however, the study investigators were not involved in caring for the majority of the infants involved in this study

since the clinical care was provided by a large pool of attending neonatologists. Another limitation of this study is the relative imbalance in the number of infants included at the two study sites, precluding meaningful inter-center comparisons. Furthermore, although the sample size was sufficient to conclusively examine the primary outcome of this study, it was not large enough to further analyze the data based on GA sub-stratification.

Conclusions

There is no statistically significant difference in successfully weaning NCPAP off in < 31 weeks GA infants between the SP versus NSP approach. Secondary outcomes such as the number of attempts and total days required for successful weaning, BPD, ROP, PVL, and LOS are also similar between the two groups, suggesting that there may be a role for implementing either SP or NSP method of weaning from NCPAP in a NICU and then optimizing the implemented weaning method in that unit.

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References

1. Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, Laptook AR, et al: Early CPAP versus surfactant in extremely preterm infants. N Engl J Med 2010; 362: 1970-1979.

2. Finer NN, Carlo WA, Duara S, Fanaroff AA, Donovan EF, Wright LL, et al: Delivery room continuous positive airway pressure/positive end-expiratory pressure in extremely low birth weight infants: a feasibility trial. Pediatrics 2004; 114: 651-657.

3. Vaucher YE, Peralta-Carcelen M, Finer NN, Carlo WA, Gantz MG, Walsh MC, et al: Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. N Engl J Med 2012; 367: 2495-2504.

4. Avery ME, Tooley WH, Keller JB, Hurd SS, Bryan MH, Cotton RB, et al: Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics 1987; 79: 26-30.

5. Van Marter LJ, Allred EN, Pagano M, Sanocka U, Parad R, Moore M, et al: Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? Pediatrics 2000; 105: 1194-201.

6. Jonsson B, Katz-Salamon M, Faxelius G, Broberger U, Lagercrantz H: Neonatal care of very-low-birth-weight infants in special-care units and neonatal intensive-care units in Stockholm: early nasal continuous positive airway pressure versus mechanical ventilation: gains and losses. Acta Paediatr Suppl 1997; 419: 4-10.

7. Poets CF, Sens B: Changes in Intubation Rates and Outcome of Very Low Birth Weight Infants: A Population-based Study. Pediatrics 1996; 98: 24-27.

8. Gittermann MK, Fusch C, Gittermann AR, Regazzoni BM, Moessinger AC: Early nasal continuous positive airway pressure treatment reduces the need for intubation in very low birth weight infants. Eur J Pediatr 1997; 156: 384-388.

9. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB, et al. Nasal CPAP or Intubation at Birth for Very Preterm Infants. N Engl J Med 2008; 358: 700-708.

10. Kirpalani H, Millar D, Lemyre B, Yoder BA, Chiu A, Roberts RS: A Trial Comparing Noninvasive Ventilation Strategies in Preterm Infants. N Engl J Med 2013; 7369: 611-620.

11. Narendran V, Donovan EF, Hoath SB, Akinbi HT, Steichen JJ, Jobe AH: Early Bubble CPAP and Outcomes in ELBW Preterm Infants. J Perinatol 2003; 23: 195-199.

12. Subramaniam P, Ho JJ, Davis PJ: Prophylactic nasal continuous positive airway pressure forpreventing morbidity and mortality in very preterm infants (Review). Cochrane Database Syst Rev 2016; DOI:10.1002/14651858.

13. Martin S, Duke T, Davis P: Efficacy and safety of bubble CPAP in neonatal care in low and middle income countries: a systematic review. 2014; DOI:10.1136/archdischild-2013-305519.

14. Davis PG, Henderson-Smart DJ: Nasal continuous positive airway pressure immediately after extubation for preventing morbidity in preterm infants (Review). Cochrane Database Syst Rev 2003; DOI: 10.1002/14651858.

15. Bamat N, Jensen EA, Kirpalani H: Duration of continuous positive airway pressure in

premature infants. Semin Fetal Neonatal Med 2016; 21: 189-195.

16. Jardine LA, Inglis GD, Davies MW: Strategies for the withdrawal of nasal continuous positive airway pressure (NCPAP) in preterm infants. Cochrane Database Syst Rev 2011 Feb 16;**(2)**:CD006979. doi: 10.1002/14651858.CD006979.

17. Amatya S, Rastogi D, Bhutada A, Rastogi S: Weaning of nasal CPAP in preterm infants: who, when and how? a systematic review of the literature. World J Pediatr 2015; 11: 212-218.

18. CPQCC Network Database Manual of Definitions For Infants Born in 2016. Calif Perinat Qual CARE Collab 2016; 15.0: 1-93.

19. Nair V, Swarnam K, Rabi Y, Amin H, Howlett A, Akierman A, et al: Effect of Nasal Continuous Positive Airway Pressure (NCPAP) Cycling and Continuous NCPAP on Successful Weaning: A Randomized Controlled Trial. Indian J Pediatr 2015; 82: 787-793.

20. Singh SD, Bowe L, Clarke P, Glover K, Pasquill A, Robinson MJ, et al. Is decreasing pressure or increasing time off the better strategy in weaning VLBW infants from nasal CPAP. European Journal of Pediatrics, Book of Abstracts European Academy of Pediatrics 2006; 165: 48.

21. Soe A: Weaning from nasal CPAP in premature infants. Inspire 2007; 5: 8-10.

22. Todd DA, Wright A, Broom M, Chauhan M, Meskell S, Cameron C, et al: Methods of weaning preterm babies <30 weeks gestation off CPAP: a multicentre randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2012; 97: F236-40.

23. Rastogi S, Wong W, Gupta A, Bhutada A, Rastogi D, Maimonides Neonatal Group:

Gradual versus sudden weaning from nasal CPAP in preterm infants: a pilot randomized controlled trial. Respir Care 2013; 58: 511-516.

24. Heath JRC, Broom M, Shadbolt B, Todd DA: CeasIng Cpap At standarD criteriA (CICADA): Implementation improves neonatal outcomes. J Paediatr Child Health 2016; 52: 321-326.

25. Broom M, Ying L, Wright A, Stewart A, Abdel-Latif ME, Shadbolt B, et al: CeasIng Cpap At standarD criteriA (CICADA): impact on weight gain, time to full feeds and caffeine use. Arch Dis Child - Fetal Neonatal Ed 2014; 99: F423-5.

Figure Legend

Figure 1. The figure shows the number of subjects evaluated, randomized and enrolled in each group, along with reasons for non-enrollment.

Figure 1: Enrollment

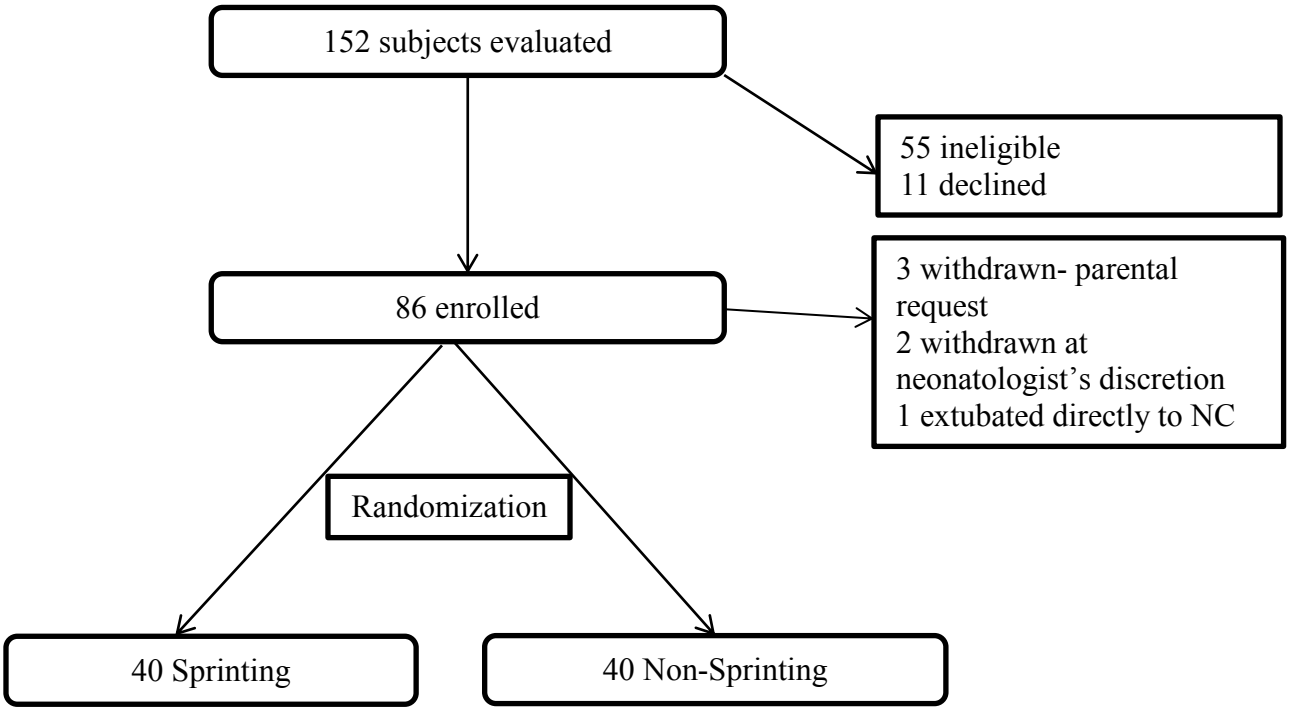

Table 1. Demographic/Clinical Data

Demographic/Clinical Characteristic	Sprinting (N=40)	Non-Sprinting (N=40)	*P* Value
Male (%)	19 (48%)	15 (38%)	NS
Ethnicity (%)			
Latino	25 (63%)	21 (53%)	NS
White	5 (13%)	9 (23%)	NS
Black	5 (13%)	10 (25%)	NS
Asian	4 (10%)	0	NS
Other	0	0	NS
Birth GA (wks)†	26.5 (23.6-30.6)	27.4 (23.9-30.7)	NS
Birth Weight (kg)†	0.95 (0.54-1.75)	0.98 (0.5-1.58)	NS
CGA-Start (wks)†	31.9 (27.7-38.4)	31.8 (28.9-35.6)	NS
Wt-Start (kg)†	1.35 (0.84-2.22)	1.32 (0.78-2.31)	NS
Age (days)-Start†	37 (3-100)	31 (3-67)	NS
CGA-End (wks)†	33.4 (28.7-41.4)	33.2 (29.9-36.6)	NS
Wt (kg)-End†	1.6 (0.98-3.12)	1.54 (0.86-2.52)	NS
Surfactant (%)	29 (73%)	25 (63%)	NS
Adequate Antenatal Steroids (%)	30 (75%)	34 (85%)	NS
Hemoglobin (gm/dL) *	10.9 ± 3.1 (9.7-11.7)	12 ± 3.3 (10.9-13)	NS
Chorioamnionitis (%)	7 (18%)	4 (10%)	NS
IUGR (%)	1 (3%)	4 (10%)	NS

CGA- Corrected Gestational Age; IUGR- Intrauterine Growth Retardation
†=Mean (Range) ; *=Mean±SD (95%CI)

Table 2: Primary Outcomes

Outcome	Sprinting (N=40)	Non-Sprinting (N=40)	*P* Value
Successful Wean off CPAP the first trial off (%)	31	30	NS
Attempts to Wean off CPAP †	1.3 (1-1.75)	1.33 (1-1.75)	NS
Days on Protocol†	7 (7-7)	7 (7-10)	NS

†=Median(IQR)

Table 3: Secondary Outcomes

Outcome	Sprinting (N=40)	Non-Sprinting (N=40)	*P* Value
BPD (%)	11 (28%)	14 (35%)	NS
ROP (%)	12 (30%)	15 (38%)	NS
PVL (%)	0	1 (3%)	NS
Length of Stay in Days†	82.5 (60.5-103.3)	78 (62-108)	NS
CGA at time of discharge/transfer†	37 4/7 (36 2/7-40 2/7)	39 (36 6/7-41)	NS

†=(Median (IQR)