Gradual Versus Sudden Weaning From Nasal CPAP in Preterm Infants: A Pilot Randomized Controlled Trial

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BACKGROUND: There is paucity of information on the weaning of nasal CPAP (NCPAP) in preterm infants. As the weaning from NCPAP can be gradual or sudden, we wanted to determine which of the 2 methods was better. METHODS: A prospective randomized trial was conducted to compare the success of weaning from NCPAP when using the sudden and gradual weaning methods in infants born ≤ 32 weeks. We also compared the weight, post-menstrual age when these infants were successfully weaned from NCPAP, and their length of stay in the hospital. RESULTS: Of the 56 infants included in the study, 28 infants were randomized to each weaning method. The gestational age, birth weight, and other clinical factors were similar between the 2 groups. There was no difference in the rate of success of initial weaning between the 2 methods ($P = .65$). The infants were successfully weaned at 33.7 ± 2.8 weeks versus 33.8 ± 2.6 weeks ($P = .93$) post-menstrual age, and at 1,736 ± 487 g versus 1,736 ± 501 g ($P = .99$) weight in the sudden wean and gradual wean groups, respectively. Length of stay was 61.3 ± 19.6 days for the sudden wean group and 66.0 ± 27.1 days for the gradual wean group ($P = .48$). CONCLUSIONS: There was no difference in the success of weaning from NCPAP between the 2 weaning methods. The weight and post-menstrual age at the time of successful NCPAP wean also did not differ between the 2 groups. These findings suggest that factors other than the method of CPAP wean, such as pulmonary maturity, may determine the success of NCPAP wean in preterm infants. *Key words: premature infants; randomized; controlled trial; weaning; nasal continuous positive airway pressure.* [Respir Care 2013; 58(3):511–516. © 2013 Daedalus Enterprises]

Introduction

Treatment of neonatal respiratory distress syndrome with intermittent positive-pressure ventilation is associated with high pulmonary morbidity. This has led to increased use of nasal CPAP (NCPAP) in preterm infants as an alternative ventilatory modality. NCPAP has been shown to decrease the incidence of bronchopulmonary dysplasia, or is comparable to mechanical ventilation with no increase in other morbidities.[1–8] In the short-term, its benefits are related to the alveolar recruitment and prevention of airway collapse. Long-term use may be associated with increase in the lung growth, as observed in animal models.[9]

There is a paucity of information on the optimal method to wean from NCPAP.[10–12] A recent study on NCPAP weaning in different neonatal ICUs (NICUs) highlighted the lack of consensus, with only 6% of the responders having a written protocol. Furthermore, there was variability in the methods used to wean infants from NCPAP by the neonatologists.[13] Using a survey, Jardine et al found that 56% of the responding neonatologists used graded time off NCPAP to wean, while the rest of the responders decreased the PEEP during weaning, or used a combination of both.[14] Since there are no written protocols, there is

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substantial inter-institutional and inter-provider variability within the same institution in the weaning practices for NCPAP.

We recently reported on factors associated with successful wean from NCPAP in preterm infants,[15] but there are no studies that have compared different methods to wean infants off NCPAP. Since sudden wean and gradual wean were the more commonly used methods,[14] we proposed to compare these 2 methods to identify whether one method was superior to the other. We hypothesized that gradual weaning using graded time off NCPAP would be more successful in weaning preterm infants from NCPAP, as compared to the sudden weaning method.

QUICK LOOK

Current knowledge

Nasal CPAP is increasingly used as the sole mode of mechanical ventilatory support in pre-term infants with respiratory distress. Nasal CPAP reduces the incidence of bronchopulmonary dysplasia, compared to intermittent positive-pressure ventilation. Nasal CPAP can be discontinued abruptly or weaned over time; the optimal method is not known.

What this paper contributes to our knowledge

Abrupt discontinuation versus gradual withdrawal with alternating nasal CPAP and spontaneous breathing had similar success. Other factors, including pulmonary immaturity and comorbidities, may play a role in weaning success, separate from the discontinuation method.

Methods

Study Population and Enrollment Criteria

A prospective randomized trial was conducted on infants born at gestational age ≤ 32 weeks admitted to the NICU at the Maimonides Infant and Children's Hospital and who required NCPAP for at least 48 hours. The study was conducted between January 2008 and March 2009. Those with chromosomal defects and severe congenital anomalies, including congenital heart disease, neurological malformations, chest wall or airway abnormalities, and lung hypoplasia, were excluded from the study. This study was approved by the institutional review board at Maimonides Medical Center and was conducted in compliance with the Health Insurance Portability and Accountability Act regulations. Informed consent was obtained from parents.

Study Protocol

We used bubble NCPAP delivered by binasal prongs (Hudson RCI, Research Triangle Park, North Carolina). NCPAP was initiated in all spontaneously breathing infants and in infants following extubation. NCPAP weaning was initiated when the infant was clinically stable on F_{IO_2} of 0.21 and at 5 cm of H_2O pressure for at least 48 hours. Additionally, there was no evidence of increased work of breathing, determined clinically by persistent tachypnea (breathing frequency > 60 breaths/min for > 2 h), marked retractions or occurrence of apneas (cessation of respiration for > 20 s associated with bradycardia or cyanosis with > 2 episodes in 12 h or > 3 in 24 h with at least one requiring bag and mask ventilation), as has been previously reported.[15] When infants were tried off NCPAP, special attention was given to upper airway suctioning and to keeping the neck in a neutral position, using a neck roll to prevent excessive flexion or extension. When the infants were ready to be weaned, the principal investigator (SR), who was not directly involved with patient care, allocated the infant to the group, utilizing the pre-prepared computer generated randomization charts. We had decided to wean off NCPAP to room air rather than weaning to nasal cannula, because of our previous experience,[15] and also because weaning supplemental oxygen completely before weaning off NCPAP reduces the total time on supplemental oxygen.[16]

In the sudden weaning group, NCPAP was removed and kept off completely. In the gradual wean group, it was cycled off for 3 hours alternating with 3 hours on for 48 hours. If tolerated, NCPAP was kept off for 6 hours and on for 3 hours for the next 48 hours. If the infant tolerated this for 48 hours, the NCPAP was discontinued. These time frames were chosen as they coincided with the 3 hour cluster nursing, which allowed detailed assessment of the neonatal respiratory status with minimal disturbance to the infant. PEEP was kept constant at 5 cm H_2O pressure during both weaning processes. Success of weaning was defined as the absence of persistent tachypnea, marked retractions or apneic episodes on room air with no ventilator support, and need for supplemental oxygen for 7 days. This time duration was chosen because frequently infants could be weaned off for shorter periods only to be placed back on NCPAP within 7 days. If the infant failed weaning from NCPAP, as defined by the criteria detailed above, the attending neonatologist, in discussion with the principal investigator, made another attempt to wean after 48 hours. There was no crossover in this study. Given the nature of NCPAP, blinding of the weaning process from the treating neonatologist was not possible.

Outcome Measures

In comparing 2 methods, the primary outcome of interest was the success rate of the first trial to wean from NCPAP. Other outcomes were the weight and post-menstrual age when infants could successfully be weaned off supplementary oxygen and from NCPAP, along with their length of stay in the hospital.

Along with birth weight, gestational age, ethnicity, and sex, weight and post-menstrual age were compared between the 2 groups at the following 4 time points: when NCPAP was started, when the infants reached F_{IO_2} of 0.21 on NCPAP, when weaning off NCPAP was initiated, and when the infant was successfully weaned off NCPAP.

The presence of antenatal factors, including the use of steroids, magnesium-sulfate, chorioamnionitis (maternal fever of > 38°C with maternal and fetal tachycardia), preeclampsia (blood pressure of > 140/90 mm Hg with proteinuria), and intrauterine growth retardation (< third percentile) were compared in the 2 study groups. In addition, we compared postnatal factors such as intubation, use of surfactant, presence of patent ductus arteriosus (diagnosed by echocardiograph), sepsis (culture positive), anemia (hematocrit of < 30% in the 1-week period prior to weaning NCPAP), gastro-esophageal reflux (diagnosed clinically with a response to H_2 blocker or proton pump inhibitor), apnea (cessation of respiration for > 20 s with bradycardia or cyanosis) > 3 times in 24 hours, with one requiring intermittent positive-pressure ventilation, and the presence of intraventricular hemorrhage (diagnosed by ultrasound). Caffeine was used to treat all infants diagnosed with apnea, and continued during the weaning phase. There were no intubations or pneumothoraces during the weaning process. We did not use any respiratory physiotherapy during the weaning protocol.

Statistical Analysis

Sample size calculation was done based on a retrospective chart review, where success rate of CPAP wean using the sudden wean method was 33%.[15] We hypothesized that the gradual wean method would be clinically significantly better if it was associated with 66% success weaning off NCPAP. To detect this difference, a sample size of 28 infants in each group provided 80% power with α set at .05. For comparison between the groups, analysis of continuous variables by using the *t* test, and of the categorical variables by applying the chi-square test, using statistics software (Stata 10, StataCorp, College Station, Texas)

Results

As shown in Figure 1, of the 124 infants ≤ 32 gestational age admitted in the NICU, 78 were eligible for the study, of which 56 were randomized to the 2 study groups. The mean gestational age of the infants in the cohort was 28.12 ± 1.67 weeks with mean birth weight of 1,108 ± 221 g, which was not statistically different from those who had not consented for the study.

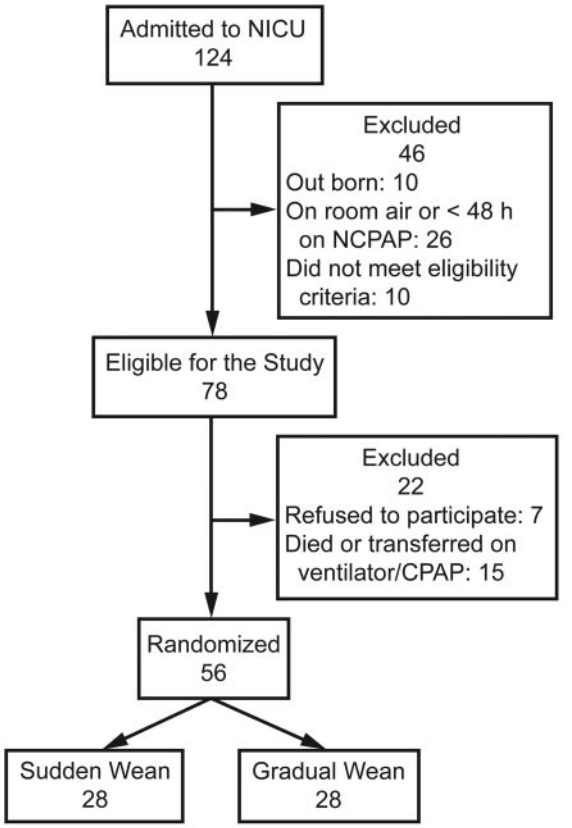

Fig. 1. Algorithm of the study design for nasal CPAP (NCPAP) wean. NICU = neonatal ICU.

Table 1 shows there were no significant differences in the demographic and clinical characteristics of the 2 study groups. There was no difference in the number of infants who successfully trialed off NCPAP in the first attempt between the sudden wean group (n = 13) and the gradual wean trial group (n = 12) (P = .65). The number of trials from NCPAP ranged from 1 to 7 (median = 2) in the gradual wean group, which did not differ from the 1 to 5 (median = 2) in the sudden wean group (P = .81).

The weight and post-menstrual age of both groups at various time points of NCPAP are shown on Figures 2A and 2B. There was no difference in the post-menstrual age (28.6 ± 1.5 weeks vs 28.9 ± 1.8 weeks, P = .58) and the weight (1,111 ± 239 g vs 1,106 ± 240 g, P = .94) between the sudden and gradual wean groups when the infants came off supplemental oxygen. The infants were successfully weaned at 33.8 ± 2.6 weeks versus 33.7 ± 2.8 weeks (P = .93) post-menstrual age, and at 1,736 ± 487 g versus 1,736 ± 501 g (P = .99) weight in

Table 1. Clinical Characteristics

	Sudden Wean (n = 28)	Gradual Wean (n = 28)	P
Weight, mean ± SD g	1,131 ± 221	1,080 ± 219	.42
Gestational age, mean ± SD weeks	28.12 ± 1.63	27.95 ± 1.76	.53
Male/female, no.	17/11	16/12	.20
Ethnicity			
White	7 (25)	7 (25)	
African American	6 (21.4)	4 (14.3)	
Hispanic	5 (17.9)	7 (25)	.57
Asian	9 (32.1)	6 (21.4)	
Prenatal steroids	23 (82.1)	22 (78.6)	.54
Preeclampsia	6 (21.4)	3 (10.7)	.44
Chorioamnionitis	1 (3.6)	1 (3.6)	.88
Intrauterine growth restriction	6 (21.4)	3 (10.7)	.44
Antenatal Magnesium	15 (53.6)	14 (50)	.99
Intubation	7 (25)	9 (32.1)	.65
Surfactant	5 (17.9)	6 (21.4)	.72
Days to reach room air CPAP, mean ± SD	2.37 ± 1.8	2.85 ± 2.5	.46
Maximum F_{IO_2}, mean ± SD	0.41 ± 0.18	0.49 ± 0.29	.16
Anemia	26 (96.2)	18 (81.8)	.09
Diuretic use	5 (17.9)	5 (17.9)	.97
Caffeine use	13 (46.4)	7 (25)	.14
Intraventricular hemorrhage	4 (14.3)	3 (10.7)	.43
Sepsis	5 (17.9)	2 (7.1)	.35
Patent ductus arteriosus	14 (50)	12 (42.9)	.66
Gastroesophageal reflux	2 (7.1)	2 (7.1)	.83
Bronchopulmonary dysplasia	1 (3.6)	2 (7.1)	.43
Discharged on O_2	0	1 (3.6)	

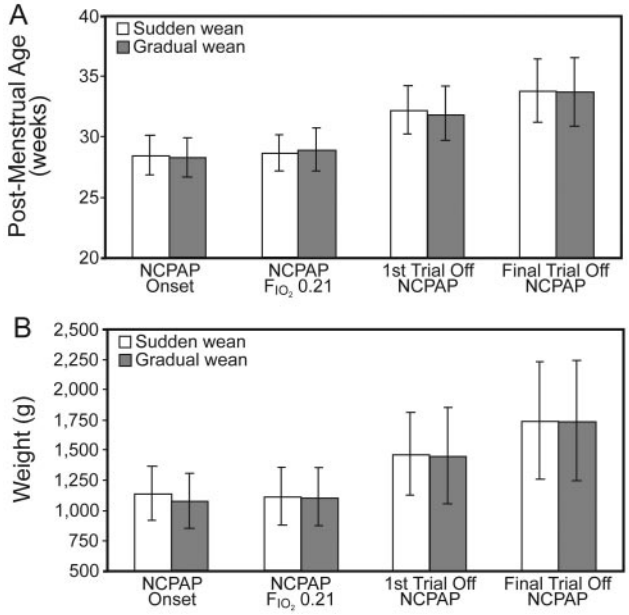

Fig. 2. Comparison of post-menstrual age in weeks (A) and weight in grams (B) at various time points of nasal CPAP (NCPAP) wean. The data are depicted as mean ± SD. There were no differences between the post-menstrual age and weight at all 4 time points.

the sudden wean and gradual wean groups, respectively. The length of stay for the sudden group (61.3 ± 19.6 d) did not differ from that for the gradual wean group (66.0 ± 27.1 d) (P = .48).

Discussion

Contrary to our hypothesis, we found no difference in the success rate of the initial trial to wean from NCPAP between the sudden and gradual weaning methods, which were started only when the infants were stable on NCPAP of 5 cm of H_2O and on F_{IO_2} of 0.21. Weight, post-menstrual age at time of successful wean, and the length of stay did not differ between the 2 methods. These findings suggest that the ability to be successfully weaned off NCPAP may be independent of the weaning method and may be a phenomenon of pulmonary maturity.

Jardine et al, in a recent review[12] based on 3 abstracts on weaning from CPAP,[17–19] identified lack of data on the clinical criteria or best strategy for withdrawal of NCPAP. These abstracts lack one or more aspects that are integral components of such comparative research. Our study is more comprehensive, as we randomized the infants in a

predetermined manner, with the person randomizing not being involved in the direct medical care. There was no clear randomization procedure in 2 of the 3 studies included in the review.[17,18] Contrary to our findings, Todd et al found that sudden wean was associated with shorter time on CPAP.[19] One potential explanation for this difference may be the lack of a standard protocol for the gradual wean method by Todd et al, which varied with the treating neonatologist. In our study, we had defined weaning strategy a priori, obviating inter-provider variation.

We used bubble NCPAP applied through binasal prongs for all our infants, which has been shown to be associated with shorter duration and better oxygenation in animal models and preterm infants.[6,20,21] In addition, while all infants in our study were on the same PEEP during weaning, this detail is lacking in the studies included in the Cochrane review.[12] Whether the differences in PEEP in addition to method of weaning play a role in the time to successful weaning from NCPAP needs to be investigated further. Moreover, we defined a successful wean attempt when the infant remained off CPAP for duration of 7 days, which was also included in the 3 studies in the Cochrane review.[17–19] This is an important consideration in defining the success of CPAP wean for future studies, as we frequently observe that infants who may have been initially weaned may still fail after a few days and require being placed back on CPAP.

We preferred gradual wean in our NICU, as there may be potential benefit of "training" the respiratory muscle to prevent fatigue. Infants who gradually wean from NCPAP have less atelectasis, compared to sudden wean, because of re-recruitment of collapsed alveoli during the cycling process.[12] Also, as the warm humidified air softens the skin over the nasal septum, making it prone to trauma,[22,23] removal of nasal prongs allowed time for the septum to dry. Furthermore, it allowed the parents an opportunity to have unhindered interaction with their infant.[24] However, there are certain physiological disadvantages of gradual weaning, as it removes the constant CPAP, which provides both static and phasic strain, helping the induction of lung growth.[9] Another disadvantage of gradual weaning in our study may be the length of the gradual wean used, which was longer than the sudden wean protocol. Since weaning was attempted again after 48 hours of failure, more trials of sudden wean protocol could be performed, as compared to gradual wean protocol, for the same time period. A shorter weaning protocol for gradual wean could have been helpful by decreasing the period of trialing from NCPAP yet continuing to provide beneficial effect of lung growth. The optimal length of the gradual weaning protocol needs to be studied further.

We found that there was a mean difference of 5 days in the length of stay in infants on gradual wean, as compared to those who underwent sudden wean. Although this difference did not reach statistical significance, it may be of potential clinical importance, as it may contribute to a shorter length of stay in the NICU. Future studies with larger study samples are needed to validate our findings.

There are other limitations in our study. Given the nature of CPAP, blinding of providers was not possible. Further, despite the availability of clinical guidelines for defining success or failure of NCPAP wean, there is a possibility that there may be subjectivity in the medical providers' decision. This subjectivity may have potentially influenced the results. Additionally, we had estimated the sample size based on the expectation of 33% success of weaning from NCPAP by sudden removal, based on our retrospective data, but in this study we observed a higher rate of success of 46%. This could have led to an underestimation of the sample size. We propose that this increase in success may have been related to greater adherence to a defined protocol, as compared to routine clinical practice, in keeping with previous reports in other clinical conditions.[25] However, given the paucity of information, our study provides pilot data on NCPAP weaning methods in infants who were stable on NCPAP of 5 cm of H_2O and on F_{IO_2} of 0.21. These findings need to be validated in larger studies.

Conclusions

In conclusion, we observed no difference in the success of weaning from NCPAP between sudden and gradual weaning methods. Our findings may be used for the development of guidelines for weaning from NCPAP in preterm infants. This information may also be used by the neonatologist to decide the correct age and weight to wean infants from NCPAP, as earlier weaning may decrease the chances of success and unduly stress the infants during the process. Future multicenter trials are needed to further investigate and support our pilot results.

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