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ORIGINAL ARTICLE

Sudden versus gradual pressure wean from Nasal CPAP in preterm infants: a randomized controlled trial

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OBJECTIVE: In preterm infants, nasal continuous positive airway pressure (NCPAP) is widely used for treatment of respiratory distress syndrome. However, the strategies for successfully weaning infants off NCPAP are still not well defined and there remains considerable variation between the methods. The objective of this study is to determine whether gradual weaning of NCPAP pressure is more successful than sudden weaning off NCPAP to room air.

STUDY DESIGN: A randomized controlled trial was conducted in a level 3 neonatal intensive care unit on 70 preterm neonates who were born between 26 and 32 weeks gestation and required NCPAP for at least 48 h. When infants were stable on NCPAP at 0.21 FiO_2 and 5 cm H_2O positive end expiratory pressure, neonates were randomized to the gradual wean group (reduction in pressure by 1 cm every 8 h until 3 cm H_20 was reached) or to sudden wean group (one time NCPAP removal to room air). The primary outcome was a success at the first trial to wean to room air. Secondary outcomes were a number of trials, and weight and postmenstrual age (PMA) at the time of successful wean. Total number of days on NCPAP and length of stay (LOS) in the hospital were also compared between the groups.

RESULTS: Of the 70 infants included in the study, 35 were randomized to sudden group and 33 infants to gradual group (2 excluded for protocol deviation). In sudden and gradual groups, 14 and 22 infants, respectively, were weaned successfully in the first attempt ($P = 0.03$). The infants were successfully weaned at 32.7 ± 1.7 weeks versus 33.1 ± 2.4 weeks ($P = 0.39$) PMA and at a weight of 1651 ± 290 g versus 1589 ± 398 g ($P = 0.46$) in the sudden and gradual groups, respectively. The total number of days on NCPAP was 27 ± 19 days versus 32 ± 24 days ($P = 0.38$) and LOS was 63 ± 25 days versus 63 ± 22 days ($P = 0.99$) in the sudden and gradual groups, respectively.

CONCLUSIONS: Gradual weaning method was more successful as compared to sudden weaning method in the initial trial off NCPAP. There was no difference in the PMA, weight at the time of successful wean, total days on NCPAP and LOS between the two groups.

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INTRODUCTION

Nasal continuous positive airway pressure (NCPAP) is widely used for the treatment of respiratory distress syndrome in preterm infants[1] and is associated with lower incidence of intubation and its related complications as compared with other modes of ventilation.[2–6] Early use of NCPAP in preterm infants is associated with decreased pulmonary[7,8] and non-pulmonary[9–11] morbidities that are associated with intubation and ventilation. It has also been shown to improve lung growth.[12] Although there are risks associated with NCPAP including nasal trauma,[13] increased incidence of pneumothorax[2] and possible association with intraventricular ventricular hemorrhage,[14,15] early weaning off NCPAP can lead to atelectasis, apnea and bradycardia, leading to prolonged use of NCPAP, or possibly intubation with subsequent mechanical ventilation and prolonged oxygen use.[1] These findings suggest that weaning off NCPAP should be planned appropriately. However, there is a lack of consensus regarding the optimal method of weaning NCPAP and timing are often implemented on *ad-hoc* basis.[16]

In recent years, investigations into the optimal method and timing of weaning off NCPAP[16,17] have highlighted the considerable variation that exists in the methods and the timing used for weaning of NCPAP. The varied weaning methods that have been used include sudden removal of NCPAP, gradual increase in time off NCPAP, gradual reduction of NCPAP pressure with or without oxygen supplementation, transition to high-flow nasal cannula (NC) or a combination of all of these methods.[18–23]

We had reported factors associated with successful wean from NCPAP in preterm infants and the clinical criteria for defining readiness to wean, successful wean and failure of wean.[24] However, there is no consensus on the optimal method of weaning. Although we have previously found no difference between sudden wean of NCPAP and a gradual cycling of time off NCPAP,[23] others have shown that sudden weaning may be associated with a shorter weaning time.[22] In the ceasing CPAP at standard criteria (CICADA) study, once stability criteria was met, NCPAP was taken off in a sudden manner and this led to shorter NCPAP weaning time, NCPAP and oxygen duration, and lower incidence of broncho-pulmonary dysplasia, as compared with gradual cycling off NCPAP with or without NC.[22,25] Conversely, Singh *et al.*[19] reported a gradual decrease in pressure of NCPAP to be better than a gradual time off NCPAP in terms of successful wean and duration of NCPAP. Based on this conflicting literature on the NCPAP wean methods, we hypothesized that gradual

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pressure wean as compared with sudden wean would be more successful in the first attempt in trialing off NCPAP. We also hypothesized that gradual pressure weaning would also be associated with shorter time on NCPAP and shorter length of stay (LOS) in the hospital.

METHODS

Study design

A prospective randomized controlled trial was conducted on preterm infants born at 26 weeks to 32 weeks of gestation at Maimonides Infant and Children's Hospital between October 2013 and November 2015. The 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. An informed consent was obtained from the parents. The trial was registered at Clinical trials as NCT02126501.

Study population

One hundred and fifty four preterm infants born at the gestational age 26 weeks to 32 weeks requiring at least 48 h of NCPAP, admitted to the neonatal intensive care unit, met the eligibility criteria (Figure 1). All infants, including those who were initially intubated and then extubated to CPAP or those who were never intubated were eligible for the study. 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. A medical provider in the infant's circle of care approached their families to ask whether they would be willing to have a research coordinator speak to them about the study. When the family agreed, one of the study authors spoke with the family and described the study along with its risks and potential benefits. The parents or legal guardians were given adequate time to reflect on the information and have any questions answered before giving consent. Once consented, the principal investigator, who was not directly involved in the patient care, included the infant in the study and allocated the infant to a study group, utilizing the pre-prepared computer-generated randomization charts.

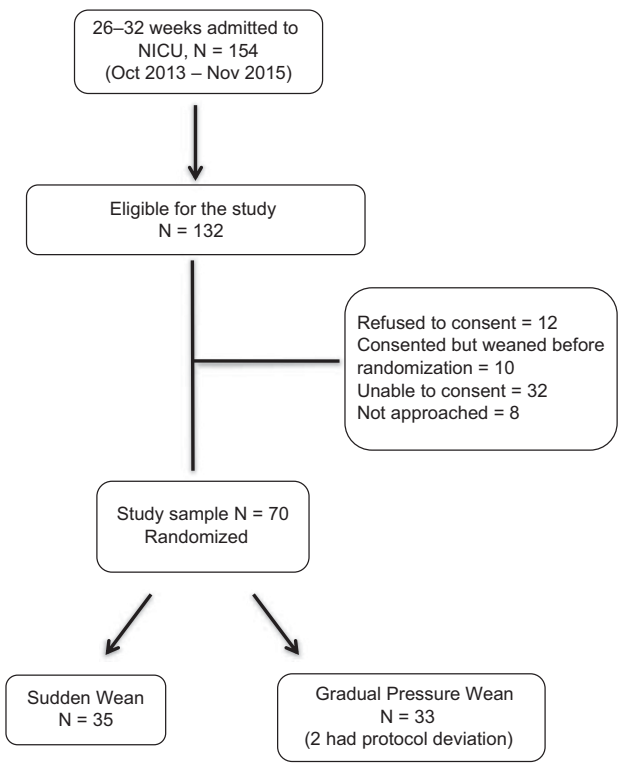

Figure 1. CONSORT flow diagram.

Study interventions

Application of NCPAP has been described earlier.[23,26] Briefly, bubble NCPAP system (Fischer Paykel, Auckland, New Zealand) was used for pressure generation and the pressure in the circuit was checked by Criterion 40 pressure monitor (Respironics-Novametrix, Wallingford, CT, USA). NCPAP weaning was initiated as per the randomization allocation, when the infant was clinically stable on FiO_2 of 0.21 and at 5 cm of H_2O pressure for a minimum of 48 h. Weaning was initiated when all other stability criteria (Table 1) were also met.

In the sudden weaning group, NCPAP at FiO_2 of 0.21 and at 5 cm of H_2O pressure was removed and kept off completely. In the gradual pressure wean group, the pressure was decreased by 1 cm of H_2O pressure every 8 h from an initial positive end expiratory pressure (PEEP) of 5 cm H_2O until a PEEP of 3 cm H_2O was reached. NCPAP was then removed and kept off completely. In this group, the total time to wean off NCPAP to room air was 24 h. The babies were not placed on any support such as NC after weaning. If the baby failed to wean on the initial attempt, repeated attempts were made in the original arm, with no crossover to the other arm after minimum of 24 h (Figure 2). Owing to the nature of NCPAP use in the neonatal intensive care unit, there was no blinding of the weaning process from the attending care teams, nursing staff, and study investigators.

Predetermined criteria (Table 2) were used to determine failure and success of the weaning trial. If the infant failed the trial, he/she would be placed back on FiO_2 of 0.21 and 5 cm of H_2O pressure. The next attempt at weaning was made after a minimum of 24 h and once the stability criteria were met again. Successful weaning was defined as the absence of persistent tachypnea, marked retractions or apneic episodes on room air without ventilator support, or need for supplemental oxygen for 7 days. The stability criteria, failure criteria and successful wean definition were available for the nursing staff as well as the clinical team at the bedside chart of the study patients.

Study outcomes

The primary outcome of interest was the success rate of the first trial of NCPAP weaning. Other outcomes of interest were the total number of days on NCPAP and the LOS in the hospital, and the weight and PMA at the following time points: starting NCPAP, reaching FiO_2 of 0.21, at first trial of weaning and at successful wean off NCPAP.

Additional clinical and demographic characteristics compared between the two groups include birth weight, gestational age, ethnicity and gender, and the presence of antenatal factors including the use of steroids, magnesium sulfate, chorioamnionitis (maternal fever of >38 °C and use of antibiotics), preeclampsia (blood pressure $>140/90$ mm Hg with proteinuria) and intrauterine growth retardation ($<$ third percentile for weight). Postnatal factors including intubation, use of surfactant, use of caffeine, presence of patent ductus arteriosus (diagnosed by echocardiogram), sepsis (blood culture positive), anemia (hematocrit $<30\%$ in the 7 days prior to weaning NCPAP), gastroesophageal reflux (diagnosed clinically with a response to H_2 blockers) and the presence of intraventricular hemorrhage Stage 3 and 4 (diagnosed by ultrasound) were also compared between the two groups.

Sample size and statistical analysis

We estimated the sample size on the basis of the previous reported success in weaning from NCPAP in the first attempt,[24] where the success rate of weaning from NCPAP during first attempt using sudden wean method was 33%. We hypothesized that the gradual pressure wean method would be clinically important if associated with 66% success in weaning off NCPAP. To detect this difference, a sample size of 35 infants in each group provided 80% power with $\alpha = 0.05$. Continuous variables were analyzed using the Student's *t*-test and the categorical variables were analyzed using the χ^2-test or Fisher's exact test, based on the distribution of the variables. All analyses were done on STATA version 14 (STATA, College Station, TX, USA).

RESULTS

Study population

Of the 154 infants admitted in the neonatal intensive care unit between October 2013 and November 2015,132 were eligible for the study. Of these, 70 babies were consented and randomized, but 2 of them were excluded due to protocol deviation (Figure 1). The

Table 1. Criteria for readiness for weaning from NCPAP for 24–48 h before weaning

1. Continuous positive airway pressure (NCPAP) of 5 cm H_20; 0.21 FiO_2
2. Normal work of breathing: no persistent tachypnea (>60 breaths for >2 h),no marked retractions
3. No apnea (cessation of respiration>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
4. Saturation >90%
5. Not currently treated for PDA or sepsis at the time of weaning
6. Tolerated time off NCPAP during nursing cluster care up to 15 min or more

Abbreviations: NCPAP, nasal continuous positive airway pressure; PDA, persistent ductus arteriosus.

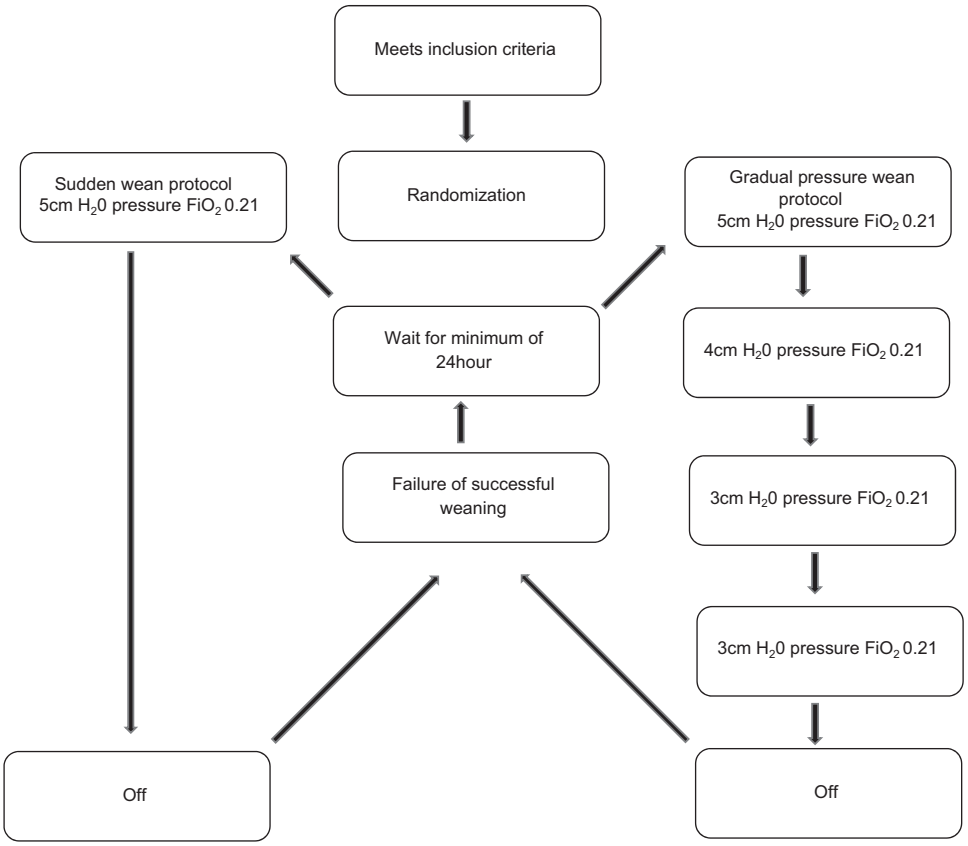

Figure 2. Details of study design.

Table 2. Criteria of failure of weaning from NCPAP present anytime till 7 days off NCPAP

1. Increased work of breathing: persistent tachypnea (> 60 for >2 h) and marked retractions
2. Apnea (cessation of respiration>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
3. Oxygen requirement >0.21 to maintain the oxygen saturations >90% for over 2 h in 24 h
4. Abnormal blood gases (2 arterial samples >2 h apart) with low pH < 7.2, PaO_2 >65 mm Hg, PaO_2 < 50 mm Hg

Abbreviations: NCPAP, nasal continuous positive airway pressure.

clinical characteristics did not differ between the sudden wean group and the gradual wean group though use of prenatal steroids, which was higher ($P=0.02$) in the gradual wean group (Table 3). Logistic regression analysis on the association of weaning method with success at the first attempt, adjusting for use of antenatal steroids was performed. The antenatal steroids were not independently associated with success of first attempt among those who underwent gradual wean ($\beta=-7.36$, (−26.73 to 12.02, $P=0.45$)). The three episodes of sepsis, two sudden group and one in gradual group were late-onset sepsis and grew *Staphylococcus* epidermidis.

Comparison of two weaning methods

More infants in the gradual wean group were successfully weaned off NCPAP as compared with the sudden wean group (22 vs 14, $P=0.03$). The median number of attempts required to be successfully off NCPAP ranged from 1 to 5 and did not differ

Table 3. Comparison of clinical characteristics of the two study groups *n* (%)

Parameter	*Sudden wean* n = *35*	*Gradual wean* n = *33*	P-*values*
Weight in gram (mean ± s.d.)	1305 ± 374	1198 ± 330	0.22
GA in weeks (mean ± s.d.)	28.7 ± 1.8	28.5 ± 1.9	0.75
Gender M:F	3:2(21/14)	7:4(21/12)	0.76
Ethnicity			0.88
White	8 (22.8)	10 (30.3)	
African American	6 (17.1)	6 (18.1)	
Hispanic	4 (11.4)	4 (12.1	
Asian	17 (48.5)	13 (39.4)	
Antenatal steroids	29 (82.8)	33 (100.0)	0.02
Chorioamnionitis	2(5.7)	2 (6.0)	1
IUGR	2 (5.7)	4 (12.1)	0.42
Intubation	14 (40.0)	7 (21.2)	0.09
Days on ventilator (mean ± s.d.)	6.13 ± 2.64	8.28 ± 8.84	0.48
Surfactant	7 (20.0)	6 (18.2)	0.85
Days to reach RA NCPAP (mean ± s.d.)	5.6 ± 12.4	5.7 ± 12.6	0.48
Anemia	30 (85.7)	29 (87.9)	1
Caffeine use	26 (74.2)	22 (66.7)	0.49
IVH	4 (11.4)	3 (9.1)	1
Sepsis	2 (5.7)	1 (3.0)	1
PDA	22 (62.8)	16 (48.5)	0.23
GERD	5 (14.3)	2 (6.0)	0.43
BPD	3 (8.6)	3 (9.1)	1

Abbreviations: BPD, bronchopulmonary disease; F, female; GA, gestational age; GERD, gastro-esophageal reflux disease; IUGR, intra-uterine growth retardation; IVH, intraventricular hemorrhage; M, male; PDA, persistent ductus arteriosus; RA, room air.

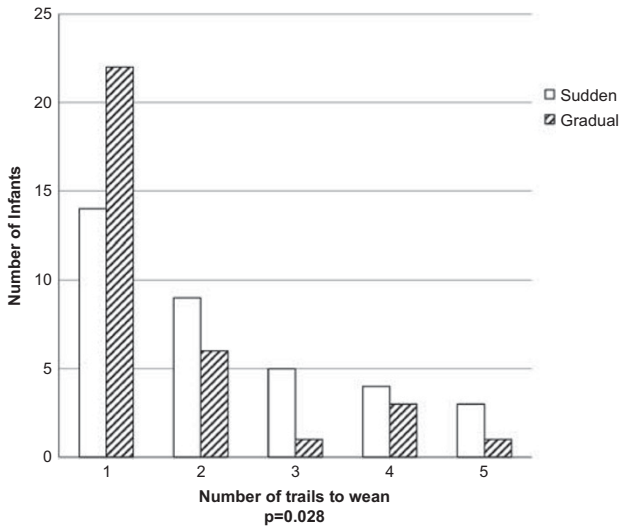

Figure 3. Number of trials to successful weaning of NCPAP by sudden and gradual pressure weaning methods.

between the two groups ($P = 0.2$), (Figure 3). There was no difference in the weight and the PMA between the sudden wean and the gradual pressure wean group at the various study time points (Figures 4a and b). The gestational age when infants came off the supplemental oxygen did not differ between the sudden and gradual wean (29.3 ± 1.9 vs 29.6 ± 2.8 weeks, $P = 0.57$). Similarly, the weight at wean off supplemental O_2 did not differ

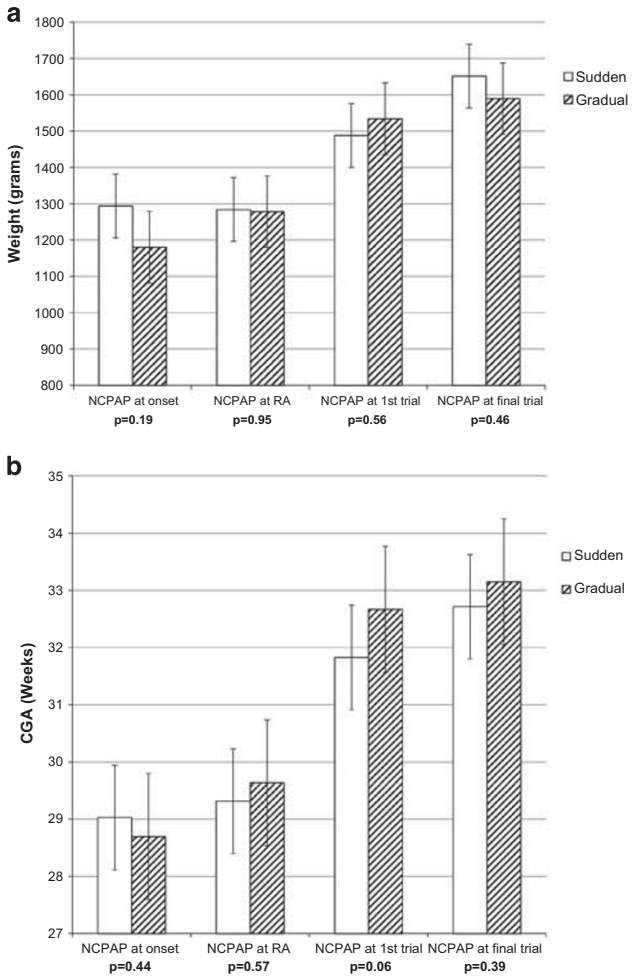

Figure 4. (**a**) Comparison of weight at various study time points between the sudden and gradual pressure wean groups. (**b**) Comparison of corrected gestational age (CGA) at various study time points between the sudden and gradual pressure wean groups.

between sudden and gradual wean (1284 ± 372 g vs 1278 ± 474 g, $P = 0.95$). The infants were successfully weaned at 32.7 ± 1.8 weeks versus 33.1 ± 2.4 weeks ($P = 0.39$) and at 1651 ± 291 g versus 1589 ± 398 g ($P = 0.46$), in the sudden wean and gradual wean groups, respectively. The LOS did not differ between the sudden wean (62.9 ± 25.4 days) and gradual wean group (62.9 ± 22.1 days) ($P = 0.99$). The total days on NCPAP in the sudden wean group (27.4 ± 19.3 days) did not differ from the gradual wean group (32.0 ± 23.7 days) ($P = 0.38$).

Comparison between those included in the trial and those who met the criteria but were not enrolled in the trial

The 62 infants who were eligible, but were not included in the trial, were found to have a higher gestational age as compared with the 70 infants who were included in the trial (29.3 ± 1.5 versus 28.6 ± 1.8 weeks, $P = 0.01$). Although the LOS was also significantly less among those not included in the trial as compared with those included in the trial (53.4 ± 2.9 vs 62.9 ± 2.8 days, $P = 0.02$), this difference was not significant when corrected for gestational age. There was an increased incidence of bronchopulmonary disease ($P = 0.03$) in those not included in the trial as compared with those included in the trial despite being significantly more mature at birth. There was no difference ($P = 0.27$) in the time spent of NCPAP in both the groups (Table 4).

Table 4. Comparison of clinical characteristics of the neonates included in the study and those infants who met inclusion criteria but not enrolled in the study *n* (%)

Parameter	*Nonrandomized* n = *62*	*Randomized* n = *70*	P-*values*
Weight mean ± s.d. (g)	1343 ± 325	1254 ± 355	0.14
GA mean ± s.d. (weeks)	29.4 ± 1.5	28.6 ± 1.8	0.01
Gender M:F	24	42	0.01
Ethnicity			0.10
White	27(43.5)	18(25.7)	
African American	8 (12.9)	12 (17.1)	
Hispanic	10(16.1)	8(11.4)	
Asian	17 (27.4)	30 (42.8)	
Antenatal steroids	49(79.0)	62 (88.6)	0.05
Chorioamnionitis	1(2.0)	4(5.7)	0.21
IUGR	5(8.1)	6 (8.6)	0.88
Intubation	12(19.3)	21(30.0)	0.13
Surfactant	8 (12.9)	13 (18.6)	0.33
Anemia	57 (91.9)	59 (84.3)	0.34
Caffeine use	35 (56.4)	48 (68.6)	0.09
IVH	8 (12.9)	7 (10.0)	0.64
Sepsis	9 (14.5)	3 (4.3)	0.05
PDA	26 (41.9)	38 (54.3)	0.11
GERD	5 (8.0)	7(10.0)	0.66
BPD	14 (22.6)	6 (8.6)	0.03

Abbreviations: BPD, bronchopulmonary disease; F, female; GA, gestational age; GERD, gastro-esophageal reflux disease; IUGR, intra-uterine growth retardation; IVH, intraventricular hemorrhage; M, male; PDA, persistent ductus arteriosus; RA, room air.

DISCUSSION

In a randomized control trial, we demonstrated that preterm infants born at 26 to 32 weeks gestation, who required NCPAP, had higher success rate at the first attempt to wean from NCPAP by gradual pressure weaning off NCPAP as compared with the sudden weaning method. There were no differences in the gestational age and weight at the time of successful wean, the total duration of oxygen use or time on NCPAP and the length of hospital stay between the two weaning methods. These findings suggest that gradual pressure wean may be associated with greater success of weaning from NCPAP.

Our findings concur with previous studies that used the gradual pressure weaning method.[19,20] Singh *et al.*[19] demonstrated that time on NCPAP was significantly less when weaning was by gradual decrease in pressure as compared with increasing time off from NCPAP. However, the authors did not comment on the success of the first trial as compared with successive attempts at weaning from NCPAP. Similarly, Soe[20] reported no significant difference in the number of NCPAP days but had a trend towards shorter time on weaning with gradual decrease in pressure. However, the details on the NCPAP delivery method, need for NC or criteria for readiness, failure and the methods used for weaning were not reported in either of the studies. Further, the time on NCPAP in both these studies was short, ranging from 6 to 15 days, which could be indicative of less severe respiratory distress during hospital stay, as compared with our study where the time on NCPAP was 3 to 4 weeks, before attempts were made to wean off NCPAP. In contrast to these previous two studies, we used well-defined and stringent criteria to define the readiness for weaning, as well as the success and failure of weaning. Furthermore, although these investigators described success of weaning as being off NCPAP for variable periods off CPAP, we had observed that infants who may have been initially stable on room air for 24 h could still fail after a few days and may require to be placed back on NCPAP.[23,24] For these reasons, our successful wean criteria was more stringent, as it was defined as NCPAP being off for longer period of 7 days. We also clearly and extensively describe details of NCPAP delivery, having used a method that has been shown to be one of the most commonly used and cost-effective methods to deliver NCPAP.[26]

Gradual decrease in pressure was more successful in the first attempt off NCPAP in our study and could be related to the prevention of atelectasis by gradually weaning pressure as compared with sudden weaning. Appropriate level of PEEP for preterm infants depends on factors influencing the underlying pathophysiology; however, gradual increase in functional residual capacity is noted from pressure of 2 to 5 cm H_2O with the normal values of healthy term infants being achieved at 5 cm H_2O.[27] Thus, 3 to 5 cm of H_2O pressure in the study may not generate adequate PEEP in each infant depending on the pathophysiology of the disease; hence, further studies on weaning should be stratified by gestational age and disease entity.

Using other methods for weaning from NCPAP, Todd *et al.*[22] in a multicenter trial found that sudden weaning was better than weaning by cycling time off and was associated with less time on oxygen and shorter LOS in the hospital. We had studied this methodology and had not observed any differences between these two methods of weaning from NCPAP.[23] The difference observed by Todd *et al.*[22] could be related to higher number of preterm infants and higher incidence of patent ductus arteriosus in the gradual time-off group in the multicenter trial.[28] Further, instead of weaning from NCPAP to room air, studies have compared NCPAP weaning with weaning to NC[29] or high flow NC.[30] Weaning to NC or high flow NC are associated with longer duration of oxygen exposure and respiratory support, and there is variable amount of residual PEEP, provided if NC is used with higher flows,[31] which may be similar to gradual pressure wean without the accurate measure of PEEP. Moreover, all the studies have lower total number of days on NCPAP as compared with our study at the time of initiation of weaning, suggesting that NCPAP may have been used after extubation, rather than as a primary mode of ventilation, as was the case in our study. The babies who initially failed on NCPAP were intubated (about 30% of infants included in the study) and the rest were managed only on NCPAP, and hence a longer duration on NCPAP in our study as compared with previously reported studies. This difference in duration on CPAP highlights that the babies in previous studies may also have had less severe respiratory disease or used CPAP during post extubation period.

There was no difference in the duration on NCPAP between the infants included in the study as compared with those who met the inclusion criteria but were not included in the study. However, the latter had significantly higher incidence of bronchopulmonary disease, despite being significantly more mature. Our findings suggest that having a protocol for readiness for weaning may also help in taking neonates off the NCPAP appropriately and may impact the incidence of bronchopulmonary disease.

Given the nature of the study, there are limitations in our study, most important being the inability to blind the providers to intervention. However, the possible impact of these lack of blinding on outcomes was decreased by utilization of strict criteria for weaning. Another disadvantage to the gradual pressure weaning method is that the protocol is inherently longer than that of sudden weaning method. This differences in the length of weaning between the two study groups are important as with failure of weaning of NCPAP, next trial of weaning could only occur after 24 h when the stability criteria were met; hence, more trials of sudden wean could be performed compared with the gradual group and could have an impact on the length on NCPAP. We did have a shorter gradual pressure weaning protocol as compared with earlier studies.[19,20,22] This helped to minimize difference in the number of trials between the two methods. The

optimal length of gradual pressure weaning method needs to be studied further. Furthermore, utilization of strict criteria for weaning improved the success from the weaning from 33% from historical data to 40% observed in this study; hence, the sample size calculated at the start of the trial was not large enough to show any differences between the two weaning methods, especially in number of trials, time on NCPAP and oxygen, and the length of stay.

We conclude that gradual pressure weaning of NCPAP was more successful in weaning off NCPAP in the first trial, but was not different in the number of attempts to wean off NCPAP, time on NCPAP and oxygen, and the length of stay when compared with sudden weaning. Our findings may be useful to develop guidelines for the readiness of weaning NCPAP and defining successful wean and failure of weaning from NCPAP. These may have an impact on the time on NCPAP and decrease inter-provider variability that is inherent to *ad-hoc* weaning. Future multicenter trials are needed for stratification by gestational age and by underlying pulmonary morbidity for validation and generalizability of our findings.

COLLABORATORS OF MAIMONIDES NEONATAL GROUP

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Trial Registration: ClinicalTrials.gov Identifier: NCT02126501

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