Pressure versus Sudden Wean from Nasal Continuous Positive Airway Pressure in Preterm Infants: A Systematic Review and Meta-Analysis

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Keywords

Nasal continuous positive airway pressure · Weaning · Preterm infant

Abstract

Background: Nasal continuous positive airway pressure (NCPAP) is a well-studied treatment for respiratory problems in preterm infants. However, the best strategy for NCPAP weaning is unknown. **Objective:** We aimed to compare the success of progressive pressure wean versus sudden wean for discontinuation of NCPAP in preterm infants. **Methods:** We conducted a systematic review and meta-analysis of publications identified by searching MEDLINE, Embase, CINAHL, and CENTRAL. Randomized controlled trials comparing pressure wean to sudden wean for NCPAP in preterm infants were included. Primary outcomes were postmenstrual age (PMA) at successful weaning and weight gain. Secondary outcomes were total duration of ventilation, success of weaning strategy on first attempt, length of stay (LOS), and bronchopulmonary dysplasia (BPD). **Results:** Two trials (422 infants) were eligible for inclusion. Pressure wean was associated with a higher PMA at weaning (33.9 ± 2.1 vs. 32.1 ± 2.0

weeks, mean difference [MD] 0.88, 95% CI 0.40 to 1.35, low quality evidence). Daily weight gain was only reported in 1 trial. Total duration of ventilation was not reported. Pressure wean was associated with higher probability of successful weaning at first attempt (risk ratio [RR] 1.25, 95% CI 1.03–1.53). However, it was not associated with LOS (MD –2.5 days, 95% CI –7.3 to 2.4) or BPD (RR 0.92, 95% CI 0.52–1.63). **Conclusion:** Sudden wean of NCPAP was associated with a lower PMA at successful wean compared to pressure wean but also with a lower rate of successful wean at first attempt, most likely because of the developmental stage at which weaning is possible.

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Introduction

Nasal continuous positive airway pressure (NCPAP) is the preferred ventilation strategy for preterm infants with respiratory distress as it preserves spontaneous breathing, does not require endotracheal intubation, and may reduce bronchopulmonary dysplasia (BPD) compared to invasive ventilation [1–3]. However, ad-

Fig. 1. Flow diagram of search results and study inclusion according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.

verse effects include gastric distension [4], pneumothorax [5], and nasal trauma [6]. While the indications to use NCPAP are well described, the optimal weaning method has not yet been identified. Delays in weaning NCPAP are associated with prolonged ventilation time and higher use of resources [7]. Nevertheless, NCPAP weaning failure is associated with more frequent and severe episodes of apnea, increased need of oxygen supplementation, increased work of breathing, and need for restarting NCPAP or potentially using mechanical ventilation [4].

Three main weaning methods have been reported: graded time of wean, sudden wean, and progressive pressure wean. A 2011 Cochrane review found that weaning NCPAP to a predefined level of pressure before stopping it completely (pressure wean) resulted in shorter duration of NCPAP, shorter length of hospital stay, and shorter time of oxygen therapy compared to strategies using graded time of wean, and recommended that future trials focus on comparing pressure wean to sudden wean [8]. A second review conducted in 2015 came to similar conclusions,

yet no studies directly comparing pressure to sudden wean had been published at that time [9, 10]. New randomized controlled trials (RCTs) comparing different methods of NCPAP weaning have since been published, and no systematic review or meta-analysis has been performed [11, 12].

The primary objective of our systematic review and meta-analysis was to evaluate the association of pressure wean compared to sudden wean from NCPAP, with post-menstrual age (PMA) at weaning and growth in preterm infants born <37 weeks who may be ready to have NCPAP withdrawn.

Materials and Methods

Protocol and Registration

This study was conducted according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [13] and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement [14]. The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (CRD42019119425).

Data Sources and Search Strategy

We searched MEDLINE, Embase, CINAHL, and the Cochrane Central Register of Randomized Clinical Trial (CENTRAL) databases from inception to October 28, 2019. In collaboration with an information specialist, we developed our search strategy that included 3 prongs linked by the boolean operator “AND.” The first and second prongs included free text and indexed terms (MeSH, Emtree, or CINAHL subject headings), respectively, related to prematurity and CPAP. These terms were linked by the boolean operator “OR” and were based on a previous Cochrane review conducted on NCPAP weaning in premature infants [8]. The third prong was composed of filters to identify RCTs. We regarded sensitivity-maximizing filters for each database as appropriate [13, 15–17]. We also hand searched citations of the recent reviews and included articles.

Eligibility Criteria

We included RCTs studying preterm infants deemed ready to be weaned from NCPAP and comparing pressure wean (discontinuation of NCPAP after progressive decrease in pressure down to a pre-defined level) to sudden wean (discontinuation of NCPAP without a prior reduction in pressure). Studies were required to report at least one of the following outcomes: PMA at successful weaning from NCPAP, measures of growth, total duration of ventilation, success of weaning strategy, length of stay (LOS), and BPD. We did not include conference abstracts. No language restriction was applied.

Study Screening and Selection

Two independent reviewers (C.L.-B. and K.B.) assessed the eligibility of studies. All citations were imported in EndNote X8 (Thomson Reuters, New York, NY, USA), and duplicates were removed. Remaining references were exported to Microsoft Office Excel 16.20 (Microsoft Corporation, Redmond, WA, USA), and title and abstracts were screened to exclude all irrelevant studies. Full texts of remaining studies were then read to confirm eligibility. Disagreement between reviewers were resolved by consensus.

Data Extraction

Data extraction was performed by 2 independent reviewers (C.L.-B. and K.B.) on a standardized form. Discrepancies were solved by discussion. For each included study, we collected methodological data, population baseline characteristics at birth and at randomization, and information concerning the interventions and outcomes.

Risk of Bias

Risk of bias for included trials were evaluated by 2 independent reviewers (C.L.-B. and K.B.) using the Cochrane Collaboration’s tool for assessing risk of bias [18].

Outcomes

The primary outcomes of this systematic review were PMA at successful discontinuation from NCPAP and growth, defined as weight gain velocity from randomization to 40 weeks PMA. Weaning was considered to be achieved at successful NCPAP discontinuation.

Secondary outcomes were: total duration of ventilation, defined as the number of days during which the infant received invasive or noninvasive respiratory support during NICU stay, success of weaning strategy at first attempt of weaning NCPAP, LOS in the NICU, and BPD, defined as the need for respiratory support or oxygen therapy at 36 weeks PMA [19].

Table 1. Characteristics of the included studies

Population	GA, weeks	Male sex	Birth weight, g	Protocol intervention (pressure)	Outcome	
					n	n
Amatya et al. [11], 2017 Infants born 26–32 weeks GA requiring >48 h of NCPAP	28.6±1.8	62%	1,253±355	When stable at 0.21 FiO ₂ and 5 cm H ₂ O PEEP, pressure was decreased by 1 cm H ₂ O every 8 h until a pressure of 3 cm H ₂ O was reached, then NCPAP was removed	33	When stable at 0.21 FiO ₂ and 5 cm H ₂ O PEEP, NCPAP was removed
Jensen et al. [12], 2018 Infants born <32 weeks GA requiring >24 h of NCPAP and >29 weeks PMA at randomization PEEP <8 cm H ₂ O	30.0±1.0	52%	1,348±357	NCPAP pressure was decreased by 1 cm H ₂ O every 24 h until a pressure of 4 cm H ₂ O was reached, then NCPAP was removed	177	NCPAP was removed without prior reduction in NCPAP pressure
FiO ₂ , fraction of inspired oxygen; GA, gestational age at birth; LOS, length of stay; NCPAP, nasal continuous positive airway pressure; PMA, postmenstrual age; PEEP, positive end-expiratory pressure.					Success rate of first trial of weaning, total number of days on NCPAP, LOS, weight gain, PMA, number of attempts to wean	
					Weight gain velocity, growth, NCPAP and oxygen supplementation duration, PMA, successful wean at first attempt, number of attempts to wean, LOS	

First author, year	Study design	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Amatya, 2017	RCT	○	○	◐	◐	◐	○
Jensen, 2018	RCT	○	○	◐	◐	◐	○

○ Low risk ◐ Unclear risk ● High risk

Fig. 2. Risk of bias of included trials.

Assessment of Quality

The grading of recommendation assessment, development, and evaluation (GRADE) framework [20, 21] was used to assess quality of evidence for each outcome of this systematic review using GRADEpro software (Evidence Prime, Inc., Hamilton, 2015, USA). Quality of evidence was evaluated by 2 independent reviewers (C.L.-B. and K.B.).

Synthesis of Results and Analysis

Meta-analyses were conducted if data from studies were available and sufficient. Mean difference (MD) was used for continuous variables. Standard mean difference was used in continuous data analysis, and risk ratio (RR) was used for dichotomous outcomes. We calculated 95% confidence intervals (CI) for each effect size estimate. We performed a random-effects meta-analysis using the DerSimonian and Laird method [22]. Statistical heterogeneity was assessed using I^2 statistics [23]. We defined $I^2 < 50\%$ as low heterogeneity. To understand sources of heterogeneity and its impact on results, we planned to perform subgroup and sensitivity analyses if data were sufficient. Due to insufficient data, we did not perform the preplanned subgroup analyses, which included gestational age at birth (< 29 weeks, ≥ 29 weeks), birth weight ($< 1,000$ g, $\geq 1,000$ g), and postnatal age at weaning (< 4 weeks, ≥ 4 weeks). Furthermore, we could not assess publication bias using funnel plots because of the limited number of studies available [24]. Data were analyzed using Cochrane Review Manager version 5.3 [25]. A two-sided p value < 0.05 was considered significant.

Results

Literature Search

We identified 939 records. After removal of duplicates, 680 unique citations were assessed for eligibility. After review of abstracts, 675 studies were removed, and 5 studies required full-text review. Of these studies, 2 met all inclusion criteria and were included in this systematic review [11, 12], representing 422 patients (Fig. 1).

Characteristics of Included Studies

The 2 included studies were published in English and included patients born at ≤ 32 weeks gestational age (Table 1)

[11, 12]. Both compared pressure wean to sudden wean but used different devices for NCPAP delivery. Amatya et al. [11] used bubble CPAP, whereas Jensen et al. [12] used the Benviste valve (Dameca, Roedovre, Denmark) to generate pressure. Criteria to initiate NCPAP weaning varied. Amatya et al. [11] initiated weaning when infants received a maximum of 21% oxygen and 5 cm H₂O of pressure, whereas Jensen et al. [12] initiated weaning when infants received $< 30\%$ oxygen and NCPAP pressure < 8 cm H₂O.

Risk of Bias

Both studies had unclear risk of bias because there was no blinding of intervention and outcome assessment (Fig. 2). The impact on outcomes was unclear.

Primary Outcomes: PMA at Successful Wean and Growth

Both studies reported PMA at weaning and were pooled in a meta-analysis. Pressure wean was associated with a significantly higher PMA at successful weaning compared to sudden wean (33.9 ± 2.1 vs. 32.1 ± 2.0 weeks, MD 0.88, 95% CI 0.40–1.35) (Fig. 3a).

Only 1 study reported measures of growth and did not find a significant difference between intervention groups (weight gain was 22 ± 6 g/kg/day in both groups, adjusted MD -0.1 , 95% CI -1.4 to 1.2) [12]. Both studies reported weight at time of successful wean, which was not significantly different between intervention groups (MD 16 g, 95% CI -87 to 118) (Fig. 3b).

Secondary Outcomes

No study reported total duration of ventilation (invasive and noninvasive combined). One study reported days on invasive ventilation (pressure wean, 8.3 ± 8.8 vs. sudden wean, 6.1 ± 2.6 days, $p = 0.48$), as well as total days on NCPAP (pressure wean, 32.0 ± 23.7 vs. sudden wean, 27.4 ± 19.3 days, $p = 0.38$) [11]. One study reported only total

a Postmenstrual age at successful NCPAP wean

b Weight at successful NCPAP wean

c Success of weaning strategy at first attempt

d Length of stay

e Bronchopulmonary dysplasia

Fig. 3. Forest plots comparing outcomes of infants weaned by pressure and sudden wean from nasal continuous positive airway pressure (NCPAP). **a, b** Postmenstrual age (a) and weight (b) at successful NCPAP wean. **c** Success of weaning strategy at first attempt. **d** Length of stay. **e** Bronchopulmonary dysplasia.

days on NCPAP after randomization in both pressure wean (median 6, IQR 2–14) and sudden wean (median 4, IQR 0–14) groups (adjusted MD 0.4, 95% CI –2.4 to 1.7) [12].

Both studies reported successful weaning at first attempt. After pooling results of all included infants, pressure wean was associated with a higher rate of success at first attempt (RR 1.25, 95% CI 1.03–1.53) (Fig. 3c). In the subgroup of infants born <28 weeks, Jensen et al. [12] reported a higher rate of successful wean at first attempt using pressure wean compared to sudden wean (41 vs. 11%, risk difference [RD] 0.31, 95% CI 0.13–0.50).

LOS was reported in both studies. Pooled data did not show a significant difference in LOS between groups (MD –2.5 days, 95% CI –7.3 to 2.4) (Fig. 3d).

Rates of BPD were reported in both studies. After pooling of results, weaning strategy was not associated with the rate of BPD (RR 0.92, 95% CI 0.52–1.63) (Fig. 3e).

Quality of Evidence

Quality of evidence was downgraded to low because of the imprecision of data caused by the small number of studies included (one level downgrade).

Discussion

In this systematic review and meta-analysis comparing pressure wean to sudden wean from NCPAP among preterm infants, we found that sudden wean was associated with a significantly lower PMA at successful wean compared to pressure wean and did not have a negative impact on LOS and risk of BPD. However, we found that pressure wean was associated with a higher rate of successful weaning at first attempt.

The association of sudden wean from NCPAP with lower PMA at successful wean is consistent with studies that compared sudden wean from NCPAP to gradual graded time off [9, 10, 26]. This suggests that sudden wean from NCPAP could reduce total duration of combined invasive and noninvasive respiratory support. However, the impact of weaning strategies on total duration of ventilation is unclear because reporting of respiratory support duration varied between trials: Amatya et al. [11] reported total days on NCPAP from birth whereas Jensen et al. [12] reported total days on NCPAP after randomization. Consequently, PMA at successful wean of NCPAP serves as a proxy for total duration of respiratory support.

The association of sudden NCPAP wean with earlier PMA at time of successful weaning is likely because gradual weaning delays the weaning once an infant is mature

enough to sustain respiratory efforts without support as assessed by the readiness criteria. Oxygen and pressure requirements used to define readiness criteria to wean NCPAP varied between the studies. The criteria used for readiness to wean may affect NCPAP weaning success rates between studies but would not affect the conclusions of the individual RCTs and this meta-analysis since the definitions used were consistent within each trial.

We did not find significant differences in LOS in the NICU and in the rate of BPD between pressure and sudden wean of NCPAP. This suggests that both methods are equally safe and do not lead to adverse clinical outcomes. Previous studies comparing sudden wean to graded time of weaning found that sudden wean was associated with shorter LOS, lower BPD rates, and shorter duration of respiratory support [8, 26, 27]. This emphasizes that pressure wean and sudden wean from NCPAP may have similar effects on these clinical outcomes. However, we cannot comment on the effect of the weaning method on weight gain as only 1 study reported this outcome [12]. Our meta-analysis did not find an association between weaning method and weight at successful weaning. However, as PMA at successful weaning was significantly lower in the sudden wean group, we would have expected that weight at successful wean would have been lower in this group, as weight is proportional to PMA in premature infants [28].

Rate of successful wean at first attempt was higher among infants exposed to pressure wean compared to sudden wean in both our meta-analysis and in the study by Amatya et al. [11], whereas Jensen et al. [12] did not find such difference in their overall population. This may be because infants in the Jensen et al. [12] study were born at an older gestational age (median 30 weeks) than infants in the study by Amatya et al. [11] (median 28.6 weeks). Pressure wean is a gradual weaning method and could have given more time to the younger infants to reach the maturation level where they could be weaned from respiratory support. This hypothesis is supported by the fact that subgroup analysis of infants born before 28 weeks of gestation in the study by Jensen et al. [12] showed that pressure wean from NCPAP was associated with higher successful weaning on first attempt compared to sudden wean. Therefore, our findings may be limited because we could not perform subgroup analysis. It is possible that pressure wean may be associated with a higher success rate at first attempt among more premature infants because they need more time to mature and attain the developmental stage at which they are able to breathe without respiratory support.

Our study presents limitations. First, there were only 2 studies that compared pressure versus sudden wean from

NCPAP, and both had a small number of patients limiting the power of the meta-analysis. Second, only 4 of our 6 predefined outcomes were reported in both trials. The lack of consistent reporting of these outcomes including weight gain velocity and total duration of NCPAP therapy highlights the need for a set of predefined outcomes for NCPAP weaning in research. Third, the unclear risk of bias of included trials limited the impact of our conclusions. However, the unclear risk of bias is due to the technical challenges associated with blinding treatment allocation. Fourth, we could not perform the pre-planned subgroup analysis due to the small number of included studies, limiting our ability to conclude on the effect of the NCPAP weaning method among extremely preterm infants. Nevertheless, our review also has important strengths. It is the first meta-analysis to compare the effects of pressure wean to sudden wean of NCPAP among preterm infants. We conducted a comprehensive search by including 4 databases and using a highly sensible search strategy. By following the Cochrane Collaboration guidelines to conduct our systematic review and meta-analysis, we ensured that our results are valid and reproducible [20, 21].

Conclusion

In summary, sudden wean of NCPAP was associated with lower PMA at successful wean compared to pressure wean, but it was associated with a lower rate of successful wean at first attempt. It was not associated with any adverse effects among preterm infants born <32 weeks GA. These findings are limited by the small number of studies, and it is unclear if they apply to extremely preterm infants born <28 weeks GA. More well-designed RCTs with larger sample sizes and standardized outcome reporting are needed to evaluate the effects of NCPAP weaning method on outcomes, particularly among extremely preterm infants.

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Statement of Ethics

This study was conducted according to the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement. Ethics approval was not required for this systematic review, as we did not use individual patient data.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.L.-B. designed the study, conducted the research, analyzed the data, and drafted the first version of the manuscript. K.B. conducted the research and acted as independent reviewer when needed. B.P. and M.B. supervised the elaboration of the study design, data collection, data analysis, and reviewed the manuscript. P.S.F. reviewed data analysis and critically reviewed the manuscript. All authors read and approved the final manuscript.

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