

Sudden Complete Versus Gradual Weaning from Nasal Continuous Positive Airway Pressure in Preterm Neonates: A Randomized Controlled Trial

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ABSTRACT

Background: Continuous positive airway pressure (CPAP) is used as respiratory support in preterm neonates; however, the best weaning method has not yet been determined. In this study, we compared sudden complete and gradual weaning from nasal CPAP (NCPAP) in preterm newborns.

Methods: This randomized controlled trial was conducted on 62 preterm neonates who were born with a gestational week of < 32 weeks and required NCPAP for at least 24 h. The neonates were stable on NCPAP at 0.21 FiO₂ and 5 cm H₂O positive end-expiratory pressure. They were randomized into two groups of gradual and sudden weaning using random numbers sheet. The primary outcome was successful weaning at the first attempt. The secondary outcomes included the number of NCPAP weaning attempts, the need for mechanical ventilation (nasal and endotracheal), duration of NCPAP, oxygenation, and length of hospital stay.

Results: According to the results, 80.6% of the patients in the sudden weaning group and 74.2% of the patients in the gradual weaning group were weaned successfully in the first attempt. However, there was no statistically significant difference between the two groups in this regard (P=0.54). Duration of NCPAP was significantly lower in the sudden weaning group, compared to that in the gradual weaning group (P<0.001). Numbers of NCPAP weaning attempts, the need for mechanical ventilation, duration of oxygenation, and hospital stay in the two groups were not significantly different.

Conclusion: There was no difference between sudden complete and gradual weaning from NCPAP in terms of treatment success and complications. The selection of the appropriate technique may depend on available equipment and treatment costs.

Keywords: Continuous positive airway pressure (CPAP), Gradual weaning, Preterm, Sudden weaning

Introduction

Continuous positive airway pressure (CPAP) is widely used in neonatal intensive care units (NICUs) for respiratory support in preterm neonates (1). Early use of nasal CPAP (NCPAP) in preterm infants with respiratory distress syndrome (RDS) can decrease the need for endotracheal intubation and mechanical ventilation (2-6). The CPAP has also been used to treat apnea in preterm infants and reduce apnea by relieving upper airway obstruction (7). The use of NCPAP after weaning preterm infants from mechanical

ventilation devices decreases the risk of atelectasis and further intubation (8). However, the NCPAP may cause certain complications, including nasal trauma, air-leak syndrome, and intraventricular hemorrhage (9, 10). In addition, it requires a larger number of health care providers and devices (11).

Therefore, it would be beneficial to wean the infant from NCPAP when it is not needed (12). However, the early weaning of infant from NCPAP may cause some complications, such as the

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episodes of apnea, bradycardia, increased oxygen demand, exacerbated respiratory distress, and the need to restart NCPAP or mechanical ventilation (1). As a result, it is highly important to find an appropriate timing and method for weaning the infant from NCPAP (12, 13).

Few studies have so far been conducted in this field, and the best strategy for weaning the infant from NCPAP remains unknown (13). Different methods have been used for weaning the infant from NCPAP with various outcomes. These methods include the sudden weaning of NCPAP, gradual weaning of NCPAP, gradual weaning of NCPAP with or without oxygenation, graded time off NCPAP, high- or low-flow nasal cannula, or a combination of these methods (15).

Amatya showed the better efficacy of gradual weaning than that of sudden weaning in terms of the primary outcomes, including successful weaning in the first attempt (16). However, Rastogi et al. found no significant difference between sudden complete and gradual weaning from NCPAP regarding the rate of success (17). Todd et al. reported that sudden weaning may lead to shorter weaning time (18). Therefore, the evidence regarding the appropriate strategy for the weaning of infant from NCPAP is inadequate. With this background in mind, we decided to compare two of the more commonly used methods, namely sudden complete weaning and gradual weaning from NCPAP, in terms of treatment success and complications.

Methods

Patients and settings

This randomized controlled trial was conducted in the NICUs of two university hospitals in Isfahan, Iran, between 2014 and 2015. The neonatologists (i.e., the first and second authors) in charge of NICU were responsible for approving each participant for entering into the study. The preterm infants younger than 32 weeks of gestation with a birth weight of $\leq 1,800$ g and 5-minute Apgar score of higher than 4, who had undergone treatment with NCPAP for at least 24 h (either as a treatment for RDS since birth or after the removal of endotracheal intubation), were included in the study.

The exclusion criteria were documented congenital heart anomalies (except for small atrial septal defect, patent foramen ovale, and patent ductus arteriosus (PDA), definitely diagnosed or possible neuromuscular diseases, lung hypoplasia, intraventricular hemorrhage (higher than grade II), thoracic or airway anomalies, other life-

threatening congenital anomalies, and the need for surgery. Besides, the patients weighing less than 750 g and those who needed mechanical ventilation before NCPAP removal were not included in the study. For both groups of study, the interventions were performed by a fellow of neonatology (i.e., the third author).

The study protocol was approved by the Ethics Committee of the Isfahan University of Medical Sciences, Isfahan, Iran (grant number: 393348), and all patients' parents signed written consent form for the participation of their child in the study. Allocation was done using random numbers generated by <https://www.randomlists.com/random-numbers>.

Intervention

For all infants, if the neonatologist permitted, the fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure (PEEP) were decreased gradually to 21% and 5 cm H₂O, respectively. To achieve this purpose, either bubble CPAP (Fisher & Paykel, Auckland, New Zealand) or Medijet REF 1000 (Medin Innovations GmbH, Puchheim, Germany) was used. For the infants with a gestational age of ≤ 28 weeks or birth weight of < 1250 g who were treated with NCPAP for RDS, and also for infants with a birth weight of < 1500 g for whom NCPAP had been started after extubation from mechanical ventilation, intravenous caffeine or aminophylline was started on NCPAP and continued until the removal of the device.

If the infant had a stable clinical condition with the FiO_2 of 21% and PEEP of 5 cm H₂O within 24 h, weaning could be done. A stable clinical condition (stability criteria) is defined as: a) respiratory rate of < 60 per min, b) absence of diaphragmatic or sternal retraction, c) less than 6 episodes of apnea (each one lasting > 20 sec) and bradycardia (< 100 beats per min) within 24 h improving with a little stimulation, d) absence of apnea requiring ventilation with positive pressure or mask, e) SpO_2 of $> 86\%$ most of the time in 24 h, f) nonuse of any drugs for PDA or in the first 48 h of sepsis, and g) tolerability of separation from CPAP for nursing care episodes (up to 15 min).

The infants with a stable clinical condition (18) were randomized into two groups. In group 1, namely the sudden complete weaning group, the infant was separated completely from the set and allowed to breathe in the room air with 21% or 40% FiO_2 and extra oxygen. The incidence of any of the following criteria was considered as weaning failure, and the infant was treated with NCPAP again: a) SpO_2 of $< 87\%$ despite an increase of up

to 60% in FiO_2 , b) an increase in respiratory work characterized by a respiratory rate of > 75 per min for > 1 h, use of accessory respiratory muscle or expiratory grunting, d) > 6 episodes of apnea and bradycardia within 24 h improving with a slight stimulation, e) incidence of one episode of severe apnea or bradycardia requiring positive pressure ventilation with mask, and f) arterial pH of < 7.2 or a PCO_2 of > 65 mm Hg (18). In the infants with weaning failure, the next attempt was pursued as soon as the clinical condition was suitable (i.e., NCPAP with a FiO_2 of 21% and 5 cm H_2O PEEP).

In group 2, namely gradual weaning group, the infant was separated from NCPAP and allowed to breathe in the room air with a FiO_2 of 21% or 40% and extra oxygen for 4 h. Then, NCPAP with 5 cm H_2O PEEP and FiO_2 of 21% was applied for 6 h. Under a stable clinical condition over 6 h, weaning was performed, and the duration of separation was increased every 4 h up to 12 h. The duration

of NCPAP between the weaning intervals was constant (i.e., 6 h).

In the next step, when the infant was weaned for 12 h and no criteria of treatment failure occurred, NCPAP was continued for additional 6 h, and then the infant was completely weaned (Figure 1). If any of the failure criteria occurred during separation or after complete weaning, NCPAP was resumed immediately. In such conditions, and after 6 h of stable clinical condition with a FiO_2 of 21% and 5 cm H_2O PEEP, the infant was weaned again. In either group, when severe irreversible apnea requiring endotracheal intubation or any failure criteria not responding to NCPAP occurred, mechanical ventilation from the tracheal airway was commenced.

Assessments

The above-mentioned stable clinical condition of an infant breathing in the room air for 72 h (i.e.,

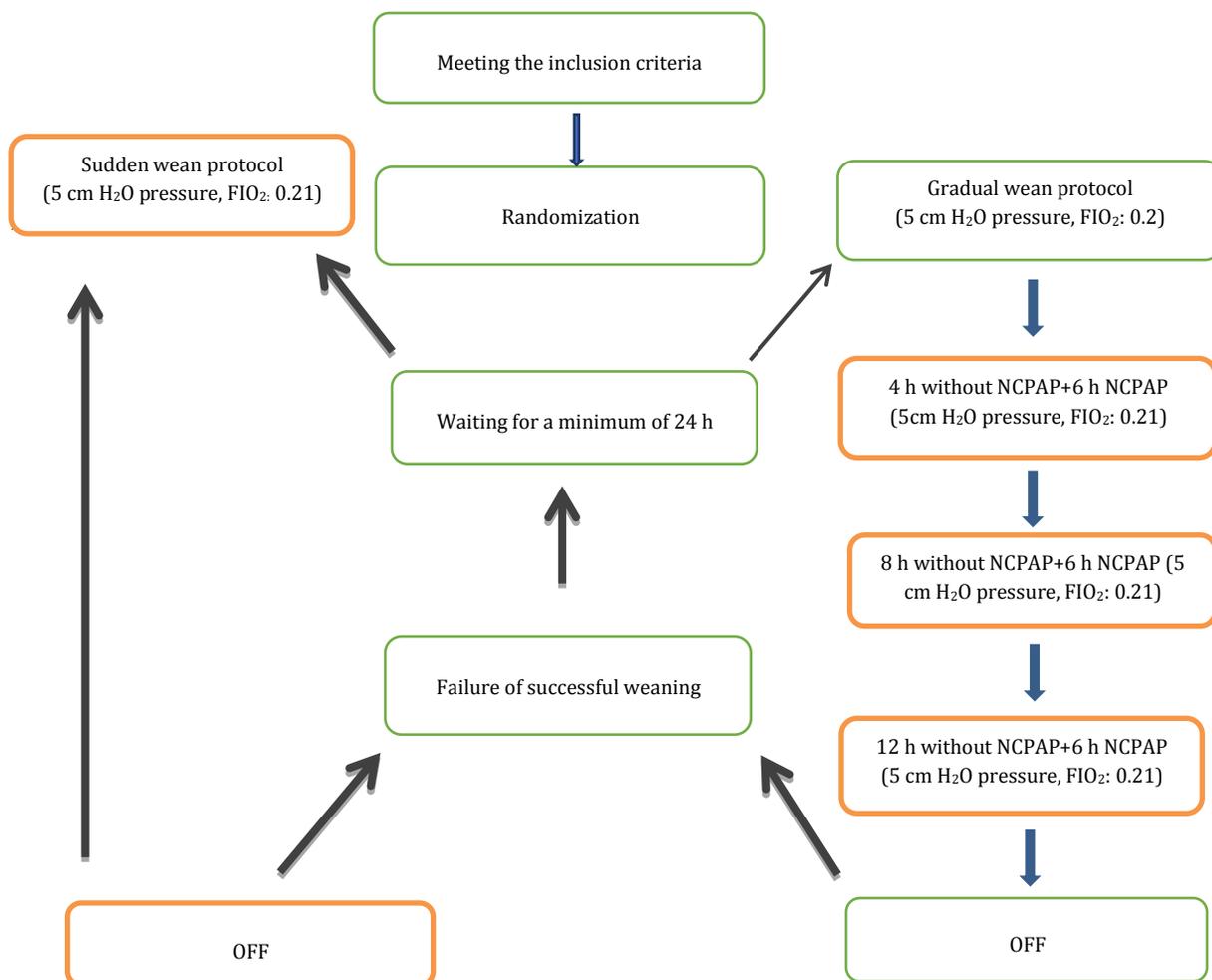


Figure 1. Details of study design

stability criteria) was considered a successful treatment (18). The primary outcome was successful NCPAP weaning in the first attempt. The secondary outcomes were the number of NCPAP separation attempts until achieving successful weaning, duration of the interval between the onset of separation and the successful one, mechanical ventilation (nasal or endotracheal) in the first week after weaning, air-leak syndromes after weaning, duration of oxygen demand, total duration of NCPAP treatment, and chronic pulmonary disease. The outcomes of interest were evaluated by a neonatologist.

Data analysis

Data analysis was performed using the SPSS, version 16.0 (SPSS Inc., Chicago, IL). The statistician performing the analysis was unaware of the treatment type used for each group. The data were expressed as mean and standard deviation or number and percentage. The data were examined for normal distribution by parametric and nonparametric tests. Intergroup comparisons were conducted by the independent sample t-test (or Mann-Whitney U test) for the quantitative variables and Chi-square or Fisher's exact test for

the qualitative variables. P-value less than 0.05 was considered statistically significant.

Results

Patients and baseline characteristics

A total of 67 preterm infants were evaluated for the inclusion criteria, 5 cases of whom were not eligible to enter the study due to cyanotic congenital heart disease (n=2), intraventricular hemorrhage grade 3 (n=1), birth weight of 600 g (n=1), and demanding myelomeningocele surgery (n=1). Sixty two patients completed the study (Figure 2). There was no difference in demographic data or baseline characteristics between the two groups (Table 1).

Study outcomes

The studied outcomes are summarized in Table 2. There was no difference in the frequency of treatment success between sudden complete weaning and gradual weaning groups (80.6% vs. 74.2%; P=0.54). In addition, the number of attempts for weaning from the set in the two groups was similar. None of the patients needed endotracheal or nasal mechanical ventilation within the first week after separation. Only one

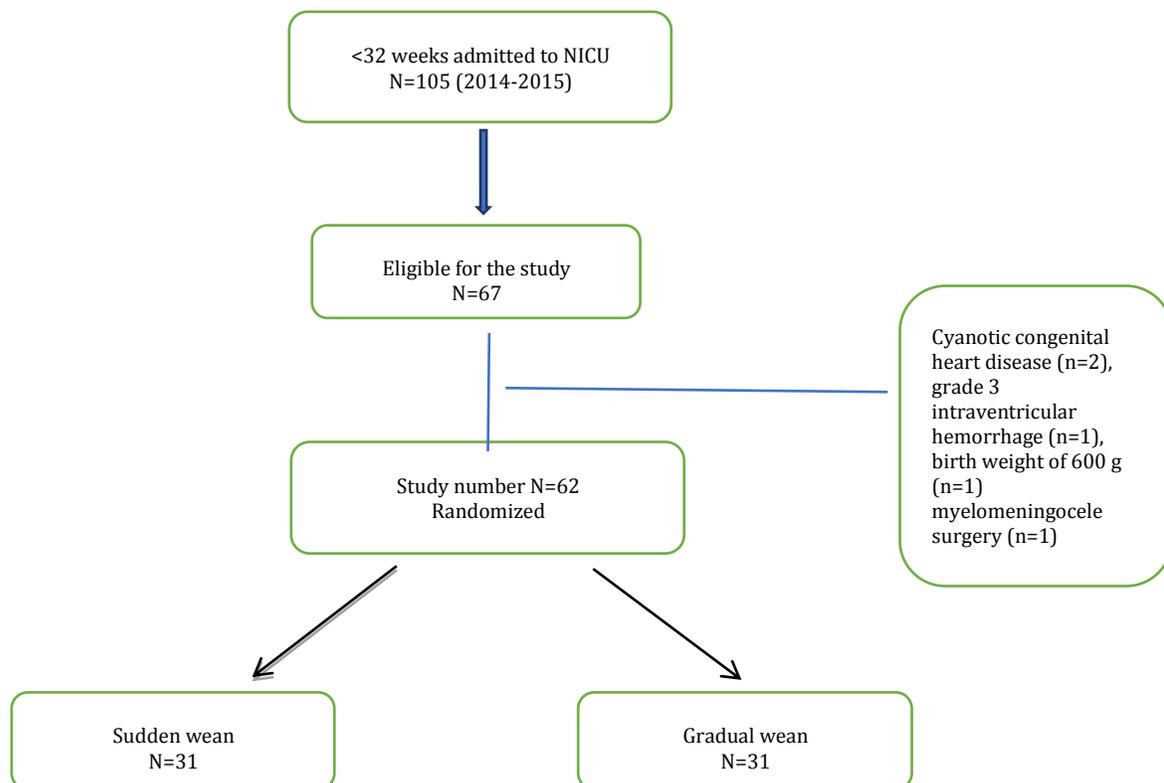


Figure 2. CONSORT flow diagram showing the study process

Table 1. Comparison of demographic data or baseline characteristics between the two groups

Demographic data	Sudden complete n=31	Gradual n=31	P-value
Gestational age (week)	30.5±2.6	30.1±1.8	0.48
Gender			0.8
Female	15 (48.38%)	14 (41.16%)	
Male	16 (51.61%)	17 (54.83%)	
Birth weight (g)	1245.3±288.8	1300.3±309.1	0.47
1st minute Apgar score	5.96±2.44	6.1±1.96	0.82
5th minute Apgar score	8±1.14	8.1±0.87	0.8
Steroid therapy	21 (67.74%)	24 (77.41%)	0.21
Surfactant therapy	22 (70.96%)	24 (77.41%)	0.31
Methylxanthine therapy	19 (61.29%)	15 (48.38%)	0.38
Patent ductus arteriosus	7 (22.58%)	2 (6.54%)	0.08
Maternal chorioamnionitis	2 (6.45%)	1 (3.22%)	0.57
Postconceptional age	31.03±2.37	31.11±3.71	0.92
Weight at weaning (g)	1266.8±318.7	1334.1±295.6	0.41
Tracheal intubation at birth	6 (19.35%)	3 (9.67%)	0.47
Mechanical ventilation	2 (6.54%)	1 (3.22%)	0.99
Ventilation duration before weaning (hour)	21.75±15.2	25.5±22.5	0.89
CPAP duration before weaning (hour)	45±28.6	68.43±43.86	0.067

CPAP: continuous positive airway pressure

Table 2. Comparison of studied outcomes between the two groups

Outcomes	Sudden weaning n=31	Gradual weaning n=31	P-value
Treatment success	25 (80.64%)	23 (74.19)	0.54
Number of attempts for weaning			0.9
2 times	5 (16.12%)	6 (19.35)	
3 times	2 (6.45%)	2 (6.45%)	
Air-leak syndrome	1 (3.22%)	0 (0%)	0.9
Oxygen requirement duration (hour)	38.22±7	37.35±5.6	0.92
Total NCPAP duration (hour)	47.9±33.1	86.45±46.9	*<0.001
Time to start oral feeding (day)	3.9±3.1	3.5±2.4	0.58
Time to complete oral feeding (day)	14±6.1	14.1±5.6	0.97
Hospital stay (day)	29.06±16.5	30.13±17	0.8

NCPAP: nasal continuous positive airway pressure

*significant difference at P<0.05

Table 3. Comparison of treatment complications between the two groups

Complication	Sudden weaning	Gradual weaning	P-value
Respiratory acidosis	2 (6.7%)	0 (0%)	0.24
Chronic pulmonary disease	8 (25%)	8 (25.8%)	0.94
FiO ₂ decrease	6 (18.8%)	9 (29%)	0.34
Increase in respiratory work	4 (12.5%)	7 (22.6%)	0.29
Recurrent apnea and bradycardia improved with stimulation	6 (18.8%)	4 (13.3%)	0.73
Recurrent apnea and bradycardia improved with bag valve mask	2 (6.5%)	1 (3.2%)	0.99

FiO₂: fraction of inspired oxygen

patient in the sudden complete weaning group experienced air-leak syndrome. There was no difference in the duration of the need for oxygen between the two groups, but the total CPAP treatment duration was lower in the sudden complete weaning group than in the gradual weaning group. There was also no difference in the time of feeding or hospital stay between the two groups (Table 2). Furthermore, there was no difference in the complications of treatment between the two groups (Table 3).

Discussion

In the present study, a comparative study regarding the sudden complete weaning and gradual weaning of premature newborns from

NCPAP was performed. For this purpose, 62 neonates with a gestational age of less than 32 weeks requiring NCPAP for at least 24 h were randomly assigned into two groups, namely gradual weaning and sudden complete weaning. The primary outcome included successful weaning in the first attempt, and the secondary outcomes were the frequency of weaning attempts, need for mechanical ventilation, length of needing NCPAP, and length of hospital stay.

Based on the results, 80.6% and 74.2% of the subjects in the gradual weaning and sudden weaning groups had successful weaning from the device, respectively; however, the difference between the two groups was not statistically significant. The frequency of weaning from

NCPAP, duration of oxygen demand, time of initiation and completion of oral nutrition, and duration of hospital stay were not significantly different between the two groups. Nonetheless, the duration of NCPAP in the sudden weaning group was significantly lower than that in the gradual weaning group.

The efficacy of gradual and sudden complete weaning techniques has been also studied in a number of previous studies, and similar results have been often obtained. In a study conducted by Amatya et al. (2017) on 70 premature infants, 14 and 22 infants in the sudden weaning and gradual weaning groups respectively had successful weaning from NCPAP with a statistically significant difference. Regarding NCPAP duration, sudden weaning and gradual weaning groups were under NCPAP for 27 and 32 days, respectively, with no statistically significant difference (16). There was also no significant difference in the duration of hospital stay between the two groups.

The results of this study showed no significant difference between the two groups with respect to the duration of hospital stay, a greater frequency of successful weaning in the gradual weaning group, and a shorter duration of NCPAP in the sudden weaning group, which are consistent with the above-cited study. In a meta-analysis (2015), weaning methods, including sudden weaning with high-flow nasal cannula (HFNC), sudden weaning, gradual weaning with HFNC, and gradual weaning alone, were compared.

The results of the mentioned study showed that the duration of respiratory support, chronic lung disease, length of hospital stay, and time of the completion of oral nutrition did not differ significantly among the investigated methods. However, in case of sudden separation in addition to HFNC, a significant decrease was reported in the time required for NCPAP (group 1: 1 day, group 2: 24 days, group 3: 15 days, and group 4: 24 days). In the rapid weaning group without HFNC, more parents asked not to use this method and wanted their baby to leave the study. The results of the above-mentioned study and the present study did not show any difference regarding the parameters between the two groups of gradual and rapid weaning (19).

In a study by Rastogi et al. (2012), the gradual and sudden separation of NCPAP did not significantly differ in terms of the success of separation, duration of admission, and duration of NCPAP. They stated that the success and treatment outcomes of NCPAP in newborns

depended on some parameters, such as fetal lung maturation (17). In the mentioned study, the duration of NCPAP in the sudden weaning group was significantly lower than that in the gradual weaning group.

In another study, Rastogi et al. reported that chorioamnionitis, intubation, use of surfactant, PDA, septicemia, anemia, apnea, gastroesophageal reflux, and intraventricular hemorrhage significantly affected weaning from NCPAP (14). In a review article, Abdel-Hady et al. (1995) suggested that the common methods of weaning from NCPAP include gradual weaning, sudden weaning, graded time off CPAP, HFNC weaning, and low-flow nasal cannula weaning, as well as a combination of the above methods.

In a review study performed by Abdel-Had, it was shown that gradual and periodic techniques increased the duration of NCPAP and hospital stay without significantly improving the success rate (15). Another review article also suggested that gradual, sudden, and periodic weaning methods are typically used to wean from NCPAP. The sudden method will reduce the duration of NCPAP, but the success and treatment outcomes do not differ significantly between different methods. The researchers argued that the success and failure criteria of various methods, including intubation, are anemia, infection, and gastroesophageal reflux (15). The results of this study are in line with the observations of the studies performed by Abdel-Hady et al. and Amatya et al.

In a study by Todd et al., the sudden method was reported to reduce the need for oxygen and the length of hospital stay when compared to the graded time off, which is not consistent with the results of our study. They argued that these observations may be due to the greater number of preterm infants and the infants with PDA in the graded time off group (18). The two groups were not identical in the mentioned study, while in the current study, the two groups were matched in terms of different parameters.

The results of the present study indicated that the two methods of weaning from NCPAP (i.e., sudden and gradual weaning) had almost no effects on the success and outcomes of treatment in newborns under NCPAP. Although the success rate of weaning was higher in the gradual weaning group, the length of the NCPAP was shorter in the sudden weaning group. Other parameters, including NCPAP side effects, duration of oxygen demand, time of onset and completion of oral nutrition, and duration of hospital stay in the two

groups, were not significantly different between the two groups.

However, our study had some limitations. First, the blinding of care providers was not possible because the study was performed in two hospitals. Secondly, although we defined the success and failure of the weaning methods by clinical guidelines, the subjectivity of the care providers' decision may have affected the final results.

Conclusion

According to the results of this study, the success rate of weaning was higher in the gradual weaning group and the length of NCPAP was shorter in the sudden weaning group. There were no differences between the sudden complete weaning and gradual weaning from NCPAP groups in terms of other parameters, including NCPAP side effects, duration of oxygen demand, time of onset, completion of oral nutrition, duration of hospital stay, and complications. Therefore, the selection of the appropriate technique may depend on available equipment and costs for both health care system and patients.

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Disclosure

The findings of this study can be used by neonatologists to decide on the proper age and weight to wean infants from NCPAP, as earlier weaning could decrease the chance of success and endanger the infants during the process. Future multicenter trials are needed to further investigate and support our pilot results.

Conflicts of interests

The authors declare no conflict of interest in this study.

References

- De Paoli AG, Morley C, Davis PG. Nasal NCPAP for neonates: what do we know in 2003? *Arch Dis Child Fetal Neonatal Ed.* 2003; 88(3):F168-72.
- Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB, et al. Nasal NCPAP or intubation at birth for very preterm infants. *N Engl J Med.* 2008; 358(7):700-8.
- Aly H. Ventilation without tracheal intubation. *Pediatrics.* 2009; 124(2):786-9.
- Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics.* 2011; 128(5): e1069-76.
- Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. *BMJ.* 2013; 347:f5980.
- Perez LA, Gonzalez DM, Alvarez KM, Diaz-Martinez LA. Nasal CPAP versus mechanical ventilation in 28 to 32-week preterm infants with early surfactant administration. *Biomedica.* 2014; 34(4):612-23.
- Davis PG, Henderson-Smart DJ. Nasal continuous positive airways pressure immediately after extubation for preventing morbidity in preterm infants. *Cochrane Database Syst Rev.* 2003; 2:CD000143.
- De Paoli AG, Davis P, Lemyre B. Nasal continuous positive airway pressure versus nasal intermittent positive pressure ventilation for preterm neonates: a systematic review and meta-analysis. *Acta Paediatr.* 2003; 92(1):70-5.
- Levene MI, Fawer CL, Lamont RF. Risk factors in the development of intraventricular haemorrhage in the preterm neonate. *Arch Dis Child.* 1982; 57(6):410-7.
- Friedman CA, Menchaca RC, Baker MC, Rivas CK, Laberge RN, Rios EH, et al. Bubble nasal CPAP, early surfactant treatment, and rapid extubation are associated with decreased incidence of bronchopulmonary dysplasia in very-low-birth-weight newborns: efficacy and safety considerations. *Respir Care.* 2013; 58(7):1134-42.
- Dunn MS, Reilly MC. Approaches to the initial respiratory management of preterm neonates. *Paediatr Respir Rev.* 2003; 4(1):2-8.
- Jardine L, Davies MW. Withdrawal of neonatal continuous positive airway pressure: current practice in Australia. *Pediatr Int.* 2008; 50(4):572-5.
- 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(1):7-13.
- Rastogi S, Rajasekhar H, Gupta A, Bhutada A, Rastogi D, Wung JT. Factors affecting the weaning from nasal CPAP in preterm neonates. *Int J Pediatr.* 2012; 2012:416073.
- Abdel-Hady H, Shouman B, Nasef N. Weaning preterm infants from continuous positive airway pressure: evidence for best practice. *World J Pediatr.* 2015; 11(3):212-8.
- Amatya S, Macomber M, Bhutada A, Rastogi D, Rastogi S. Sudden versus gradual pressure wean from Nasal CPAP in preterm infants: a randomized controlled trial. *J Perinatol.* 2017; 37(6):662-7.
- Rastogi S, Wong W, Gupta A, Bhutada A, Deepa R, Maimonides Neonatal G. Gradual versus sudden weaning from nasal CPAP in preterm infants: a pilot randomized controlled trial. *Respir Care.* 2013; 58(3):511-6.

18. 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 multicenter randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed.* 2012; 97(4):F236-40.
19. Tang J, Reid S, Lutz T, Malcolm G, Oliver S, Osborn DA. Randomised controlled trial of weaning strategies for preterm infants on nasal continuous positive airway pressure. *BMC Pediatr.* 2015; 15:147.