Noninvasive Ventilation Strategies for Early Treatment of RDS in Preterm Infants: An RCT

Vincenzo Salvo, MD[a], Gianluca Lista, MD[b], Enrica Lupo, MD[b], Alberto Ricotti, MD[c], Luc J.I. Zimmermann, MD, PhD[d], Antonio W.D. Gavilanes, MD[d,e], Ignazio Barberi, MD, PhD[a], Micaela Colivicchi, MD[c], Francesca Temporini, MD[c], Diego Gazzolo, MD, PhD[c]

abstract

BACKGROUND AND OBJECTIVES: There is evidence that new methods of noninvasive ventilation (NIV) support have significantly changed respiratory distress syndrome (RDS) management in preterm infants. Further perspectives for neonatologists involve the assessment of different NIV strategies in terms of availability, effectiveness, and failure. This study evaluates the efficacy of 2 different NIV strategies for RDS treatment in very low birth weight (VLBW) infants: nasal synchronized intermittent positive pressure ventilation (NSIPPV), which is a modality of conventional ventilation with intermittent peak inspiratory pressure, and bilevel continuous positive airway pressure (BiPAP), not synchronized, with 2 alternate levels of continuous positive airway pressure.

METHODS: We conducted a 2-center randomized control study in 124 VLBW infants (<1500 g and <32 weeks of gestational age) with RDS who received NIV support (NSIPPV, $n = 62$; BiPAP, $n = 62$) within 2 hours of birth. We evaluated the performance of NIV strategies by selected primary outcomes (failure rate and duration of ventilation) and secondary outcomes.

RESULTS: The number of failures and duration of ventilation support did not differ between NSIPPV and BiPAP strategies ($P > .05$ for both). Moreover, no differences between groups were found regarding secondary outcomes ($P > .05$ for all).

CONCLUSIONS: The present data show no statistically significant differences between NSIPPV and BiPAP strategies in terms of duration of ventilation and failures, suggesting that both NIV techniques are effective in the early treatment of RDS in VLBW infants. Further randomized investigations on wider populations are needed to evaluate the effect of NIV techniques on long-term outcomes.

WHAT'S KNOWN ON THIS SUBJECT: Noninvasive ventilation (NIV) reduced the need of intubation in preterm infants with RDS. However, randomized studies comparing nasal synchronized intermittent positive pressure ventilation and bilevel continuous positive airway pressure are still lacking.

WHAT THIS STUDY ADDS: The present study shows no differences in short-term outcomes between 2 different NIV strategies, nasal synchronized intermittent positive pressure ventilation and bilevel continuous positive airway pressure, in preterm infants for the initial treatment of RDS.

[a]*Neonatal ICU, "G. Martino" University Hospital of Messina, Italy;* [b]*Neonatal ICU, V. Buzzi Children's Hospital, Milan, Italy;* [c]*Neonatal ICU, C. Arrigo Children's Hospital, Alessandria, Italy;* [d]*Department of Pediatrics and Neonatology, School for Oncology and Developmental Biology (GROW), Maastricht University Medical Center, Maastricht, Netherlands; and* [e]*Institute of Biomedicine, Catholic University of Guayaquil, Ecuador*

Dr Salvo designed the study, participated in patient recruitment, data analysis, and writing the manuscript, and submitted the final version; Dr Lista designed the study and participated in patient recruitment, data collection, and writing the manuscript; Dr Lupo participated in patient recruitment, data collection, and writing the manuscript; Dr Ricotti participated in the design of the project, patient recruitment, and writing the manuscript; Dr Zimmermann supervised project design and data collection and participated in writing the manuscript; Drs Gavilanes and Barberi supervised project design and participated in writing the manuscript; Drs Colivicchi and Temporini participated in patient recruitment and data collection and analysis; Dr Gazzolo (project leader) participated in data analysis and wrote the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This trial has been registered at www.clinicaltrials.gov (identifier NCT02259400).

www.pediatrics.org/cgi/doi/10.1542/peds.2014-0895

DOI: 10.1542/peds.2014-0895

Accepted for publication Dec 8, 2014

Address correspondence to Diego Gazzolo, MD, PhD, NICU, C. Arrigo Children's Hospital, Spalto Marengo 46, 15100 Alessandria, Italy. E-mail: dgazzolo@hotmail.com

In recent decades, considerable changes have been made in the management of respiratory distress syndrome (RDS), supporting the notion that appropriate perinatal management can be effective by minimizing the use of mechanical ventilation (MV) in very low birth weight (VLBW) infants. In particular, antenatal steroid prophylaxis, accurate delivery room and respiratory management with early nasal continuous positive airway pressure (NCPAP), surfactant replacement in the early phase of RDS, the INSURE (intubation, surfactant extubation) procedure, and the increased use of noninvasive ventilation (NIV) have been shown to improve respiratory outcome.[1–5]

The hypothetical advantages of NIV, compared with invasive MV, consist in the possibility to reduce barotrauma, biotrauma, and ventilator-induced lung injury. Data on NIV support, such as nasal intermittent positive pressure ventilation (NIPPV), nasal synchronized intermittent positive pressure ventilation (NSIPPV), and bilevel continuous positive airway pressure (BiPAP), are still controversial. On the one hand, NSIPPV/NIPPV has shown promising short- and long-term respiratory outcomes compared with NCPAP or MV.[6–10] On the other hand, Kirpalani et al found no significant differences between NCPAP and NIV strategies (ie, NSIPPV/NIPPV/BiPAP) in a wider study population, in terms of mortality or occurrence of bronchopulmonary dysplasia (BPD).[11] In this regard, Roberts et al described several discrepancies among studies previously conducted (ie, recruited populations, ventilation modalities, devices used, synchronization systems, and clinical applications) and concluded that, at this stage, no clear advantages were detectable for NIPPV or BiPAP over NCPAP in reducing mortality or BPD.[12] Moreover, no studies elucidating any differences between NSIPPV and BiPAP, used as the primary mode of ventilation for RDS, are yet available, except for a nonrandomized study.[13]

Therefore, the present randomized study aimed to investigate the effectiveness of these 2 different NIV strategies: NSIPPV, synchronized with an intermittent positive pressure, and BiPAP, nonsynchronized with 2 alternate levels of continuous positive airway pressure (CPAP), as the primary mode of ventilation in the respiratory management of RDS in VLBW infants in terms of duration and failure of NIV support and of selected secondary outcomes.

METHODS

We conducted a randomized study in 124 VLBW infants, admitted in 2 NICUs (C. Arrigo, Children's Hospital, Alessandria, Italy, and V. Buzzi, Children's Hospital, Milan, Italy) from January 2010 to December 2012, delivered before 32 weeks of gestational age (wGA) with a birth weight <1500 g (Fig 1). Approval was obtained from the respective local ethics committees. Informed and written consent was obtained, before delivery, from all parents of the patients before inclusion in the study.

The protocol for delivery room management, RDS treatment, devices and interfaces used, and ventilator adjustment were the same for the 2 centers. Infants who had signs of RDS at birth were treated with sustained lung inflation (SLI)[14] and NCPAP in addition to the American Academy of Pediatrics recommendations.[15]

The respiratory strategy for RDS treatment in the newborns was as follows. In the delivery room, after oropharyngeal and nasal suctioning, pressure-controlled SLI (25 cmH_2O) was performed for 15 seconds using a neonatal mask and a T-piece ventilator (Neopuff Infant T-Piece Resuscitator, Fisher & Paykel, Auckland, New Zealand), followed by the delivery of 5 cmH_2O NCPAP.[16] The SLI maneuver was repeated in patients in whom respiratory and/or heart failure persisted. After failure of the second SLI maneuver, infants were intubated. In both groups, neonatal care was started at the lowest oxygen concentration, between 0.21 and 0.4 fraction of inspired oxygen (FIO_2), to maintain arterial oxygen saturation (SaO_2) of 85% to 93%. All enrolled infants were transferred to the NICU with NCPAP support (5 cmH_2O). Further support depended on gestational age (GA):

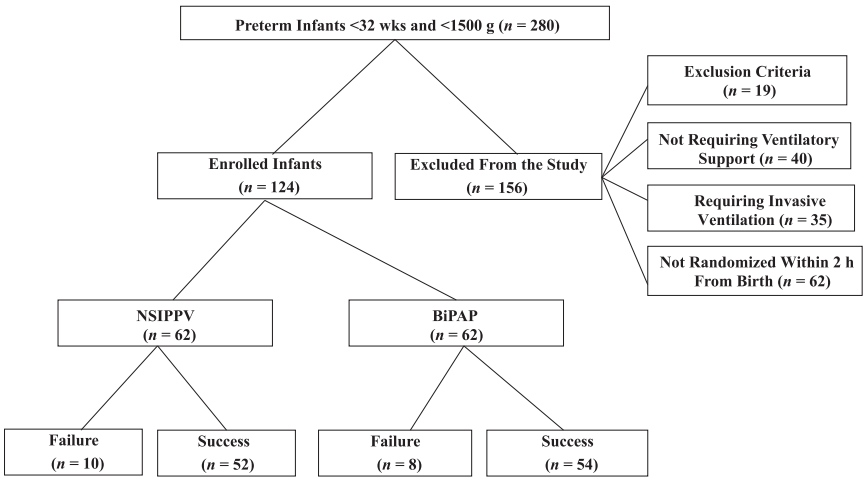

FIGURE 1
Flow chart describing recruitment.

1. Newborns ≤26 wGA received a prophylactic replacement of surfactant with INSURE in the first 2 hours of life. After INSURE, the infants were switched to either BiPAP or NSIPPV.
2. Newborns >26 and ≤29 wGA received BiPAP or NSIPPV in the first 2 hours of life.
3. Newborns >29 wGA not requiring or positively responding to the initial resuscitation maneuver were maintained on NCPAP support until arrival at the NICU; after 2 hours from birth, if they did not show any signs of RDS, NCPAP was stopped. BiPAP/NSIPPV was performed if clinical and blood gas analysis patterns were suggestive of RDS as follows: (a) need of F_{IO_2} >0.4 and/or (b) pH <7.20 and/or P_{O_2} <50 mm Hg and/or P_{CO_2} >65 mm Hg and (c) clinical patterns of RDS characterized by retractions and/or dyspnea. Apnea, defined as ≥4 episodes/hour or need for mask ventilation ≥2 times/hour, was another criterion to start NIV support.

Newborns complicated by RDS requiring NIV support within 2 hours from birth but not intubated were allocated by use of computer-generated random numbers to receive either NSIPPV (n = 62) or BiPAP (n = 62). Apneic or severely depressed newborns requiring MV within 2 hours from birth were excluded from the study and started on MV.[17]

BiPAP

BiPAP support was delivered using the Infant Flow-driver device (Infant Flow System, Viasys Corp, Yorba Linda, CA). We used the short binasal prongs as interface (CareFusion, Yorba Linda, CA) with different sizes according to weight. This method of nonsynchronized ventilation support provides 2 alternate levels, lower and higher, of CPAP; the newborn can breathe spontaneously on these 2 levels to create 2 different functional residual capacities (FRCs). The initial ventilator parameters were lower and higher, CPAP levels 4 to 6 cmH_2O and 8 to 9 cmH_2O, respectively; a $time_{high}$ of 1 second; and a pressure exchange rate of 20/minute, with the lowest adjusted F_{IO_2} to maintain an Sa_{O_2} of 88% to 93%. Respiratory settings (CPAP lower maximum 7 cmH_2O, CPAP higher maximum 10 cmH_2O, pressure exchange rate max 30/minute) were adjusted to guarantee blood gas analysis within normal ranges. Weaning was started with a progressive reduction of the set pressure exchange rate (minimum 15 pressure exchanges/minute), followed by a reduction of the higher CPAP level to 6 cmH_2O and the lower CPAP level to 4 cmH_2O. BiPAP was stopped when infants showed no signs of RDS with F_{IO_2} <0.30.

NSIPPV

NSIPPV support was delivered with a nasal ventilator device (Giulia, Ginevri, Rome, Italy) that detects the inspiratory effort by means of a pneumotachograph equipped with a fixed orifice (2-mm diameter for low birth weight infants). This is a conventional strategy of synchronized ventilation provided by nasal interface, with short binasal prongs (NIV set, Ginevri, Rome, Italy) of different sizes according to weight. The inspiratory flow was detected as a pressure change across the resistance, positioned proximally to the nasal interface. The initial ventilator parameters were positive-end expiratory pressure (PEEP) 4 to 6 cmH_2O; peak inspiratory pressure (PIP) 15 to 20 cmH_2O; inspiratory time 0.3 to 0.4 second; flow rate 6 to 10 L/minute; respiratory rate (RR) 40 breaths per minute with the lowest adjusted F_{IO_2}, to maintain an Sa_{O_2} of 88% to 93%. Respiratory settings (PIP maximum 25 cmH_2O, PEEP maximum 7 cmH_2O, RR maximum 60 breaths per minute) were adjusted to guarantee blood gas analysis within normal ranges. The highest trigger sensitivity avoiding autotriggering was selected. Weaning from NSIPPV was performed with a reduction of RR to 15 breaths per minute with a PIP of 10 to 15 cmH_2O and a PEEP of 4 cmH_2O and was stopped when infants showed no signs of RDS with F_{IO_2} <0.30.

Failure Criteria

NIV failure was defined when 1 or more of the following criteria persisted or recurred, after a surfactant dose (maximum 3 doses) or within 12 hours from previous administration: (1) hypoxia (F_{IO_2} requirement >0.40), (2) acidosis (pH <7.20) and hypercarbia (P_{CO_2} >65 mm Hg), and (3) apnea as ≥4 episodes/hour or the need for mask ventilation ≥2 times/hour. We also considered necrotizing enterocolitis (NEC), bowel perforation, and hemodynamic instability conditions for NIV failure.[18]

Surfactant Administration

According to the protocol of respiratory management, the first dose of surfactant was administered at 200 mg/kg (Curosurf, Chiesi, Parma, Italy). Additional doses of surfactant were given at 100 mg/kg, at least 12 hours after previous administration. After INSURE, newborns received the same NIV support device as before.

All newborns were treated with caffeine (caffeine citrate 20 mg/kg loading dose; 5 to 10 mg/kg/day maintenance).

Monitoring Parameters

Newborns were monitored by using pre-postductal Sa_{O_2} monitoring (Masimo Datascope Radical, Masimo Corporation, Irvine, CA). For each infant, the following variables were recorded: GA, BW, gender, main maternal pregnancy diseases, mode of delivery, and Apgar scores at 1 to 5 minutes. At study entry, F_{IO_2}, mean airway pressure (MAP), Sa_{O_2}, pH, and P_{CO_2} were recorded.

Primary Outcomes

The primary end points were the duration of NIV support and failure rate.

Secondary Outcomes

Secondary end points were duration of respiratory support, incidence of pneumothorax (PNX), occurrence of moderate/severe BPD, incidence of intraventricular hemorrhage (IVH) more than second degree, periventricular leukomalacia (PVL), need for second/multiple surfactant doses, need for postnatal glucocorticoid treatment, persistence of patent ductus arteriosus (PDA) requiring pharmacological treatment, retinopathy of prematurity (ROP) more than second degree, NEC, late-onset sepsis (LOS), death, and days to regain BW. Moderate/severe BPD was defined according to the classification of Jobe and Bancalari,[19] IVH was classified according to Papile et al,[20] and ROP was graded according to the criteria established by the International Committee for Classification of ROP.[21]

Statistical Analysis

For the calculation of sample size, we used duration of ventilation as the main primary outcome. As no basic data are available for this high-risk population, we were able to retrieve the duration of ventilation by the 2 different NIV strategies from the database of our 2 NICUs. These data were used for the power calculation. We assumed a difference of 24 hours between the 2 groups in the duration of NIV as clinically relevant. At a confidence level $\alpha = 0.05$ and power level of 0.80, we needed 62 patients for each group.[22] The sample size was calculated by using nQuery Advisor (Statistical Solutions, Saugus, MA), version 5.0.

Data were reported as means and SD and median and interquartile ranges for continuous variables, whereas absolute and relative frequencies were used for categorical variables.

Parameters of the 2 groups were compared using Student t or Mann-Whitney U 2-sided tests for continuous variables and χ^2 or Fisher exact test for categorical variables. $P < .05$ was considered statistically significant, and all P values were based on 2-tailed tests. Statistical analysis was performed by using SPSS for Windows (SPSS, Chicago, IL).

RESULTS

Table 1 shows the perinatal characteristics in the studied groups. No significant differences ($P > .05$) were found between NSIPPV and BiPAP groups for wGA, BW, gender, incidence of cesarean delivery, premature rupture of membranes, evidence of chorioamnionitis, occurrence of pregnancy hypertension requiring antihypertensive agent treatment, abruptio placentae, occurrence of multiple pregnancies, complete course of prenatal glucocorticoids prophylaxis, and Apgar scores at 1 and 5 min. No differences were shown regarding blood gas analysis, FIO_2, SaO_2, pH, and PCO_2 at study entry. We observed a significant difference in MAP that was higher in the NSIPPV group than the BiPAP group, depending on the initial ventilator settings.

Table 2 shows primary and secondary outcome characteristics. No significant differences were found between groups in terms of duration of ventilation on NIV support and incidence of failure. Moreover, there were no significant differences in the incidence of postnatal death, moderate/severe BPD, PNX, IVH, PVL, postnatal glucocorticoid administration, multiple surfactant doses, PDA, ROP, NEC, LOS, or time to regain BW. PNX occurred in 6 cases (NSIPPV, $n = 2$; BiPAP, $n = 4$) and represented a cause of NIV failure in 3 cases (NSIPPV, $n = 2$; BiPAP, $n = 1$).

In 18 of 124 infants (NSIPPV, $n = 10$; BiPAP, $n = 8$), NIV support failed. The causes were early-onset sepsis (NSIPPV, $n = 5$; BiPAP, $n = 3$), pulmonary hypertension (NSIPPV, $n = 5$; BiPAP, $n = 4$), hypoxia and hypercapnia (NSIPPV, $n = 2$; BiPAP, $n = 4$), hypoxia alone (NSIPPV, $n = 3$; BiPAP, $n = 3$), PDA (NSIPPV, $n = 1$), NEC (BiPAP, $n = 2$), and PNX (NSIPPV, $n = 2$; BiPAP, $n = 1$). The timing of NIV failure did not differ between studied groups (median [25th to 75th centile] for NSIPPV, 36 hours [17 to 72]; for BiPAP, 34

TABLE 1 Perinatal Characteristics of Preterm Infants Supported by NSIPPV or BiPAP

	NSIPPV ($n = 62$)	BiPAP ($n = 62$)	P
BW, g	1106 ± 276	1165 ± 275	.23
GA, wks	28.6 ± 2.1	28.8 ± 2.2	.66
GA ≤26 wks	9	9	.999
GA >26 and ≤29 wks	33	32	.999
GA >29 wks	20	21	.999
Male/female	27/35	25/37	.85
Small for GA	14	12	.82
Cesarean delivery	38	47	.12
Preterm premature rupture of membrane	13	20	.22
Chorioamnionitis	10	12	.63
Pregnancy-induced hypertension requiring treatment with antihypertensive agents	13	20	.22
Abruptio placentae	10	10	.999
Twins	10	15	.37
Prenatal steroids completed course	55	57	.76
Apgar score at 1 min	7 ± 1	7 ± 1	.999
Apgar score at 5 min	8 ± 1	8 ± 1	.999
Sao_2 at study entry, %	86 ± 12	87 ± 14	.67
FIo_2 requirement at study entry	0.32 ± 0.04	0.35 ± 0.05	.78
MAP at study entry, cmH_20	7.6 ± 1.0	6.2 ± 1.2	<.01
pH at study entry	7.21 ± 0.15	7.23 ± 0.10	.38
pCO_2 at study entry, mmHg	54 ± 9	53 ± 8	.51

Data are presented as the mean ± SD or *n*.

TABLE 2 Primary and Secondary Outcomes in Preterm Infants Supported by NSIPPV or BiPAP

	NSIPPV (n = 62)	BiPAP (n = 62)	*P*
Primary outcomes			
Nasal ventilation support, h	89 (61–143)	87 (48–134)	.45
Failure of nasal ventilation support	10	8	.80
Secondary outcomes			
Death	0	2	.49
Moderate/severe BPD	7	7 (*n* = 60)	1.00
PNX	2	4 (*n* = 60)	.43
IVH >2nd degree	2	2 (*n* = 60)	1.00
PVL	2	4 (*n* = 60)	.43
Postnatal glucocorticoids	5	5 (*n* = 60)	1.00
PDA	18	14 (*n* = 60)	.54
ROP >2nd degree	2	3 (*n* = 60)	.68
NEC	0	2 (*n* = 60)	.49
Multiple surfactant doses	21	18 (*n* = 60)	.97
Surfactant, >26 wGA	19 (*n* = 53)	21 (*n* = 52)	.78
Early-onset sepsis	13	15 (*n* = 60)	.67
LOS	21	14 (*n* = 60)	.23
Time to regain BW, d	14 ± 4	13 ± 4	.17

Data are presented as the median (25th to 75th centile), *n*, or mean ± SD.

hours [19 to 65]) ($P > .05$) (Table 3).

We did not find statistically significant differences in the incidence of failure either between the 2 study groups ($P > .05$ for all) or between failure subgroups after stratification for wGA (Table 3). In addition, infants who failed did not significantly differ in baseline characteristics from infants who did not fail on NIV.

DISCUSSION

In the last decade, new therapeutic strategies and technological advances have considerably changed RDS treatment in VLBW infants. New delivery room management and early NIV support significantly contributed to a sensible decay in the need for MV support.[23–28] Thus, further perspectives for neonatologists involve the assessment of different NIV strategies in terms of availability, effectiveness, and failure.

In the present 2-center randomized study, we found no differences in primary and secondary end points between 2 different NIV strategies (ie, NSIPPV and BiPAP) performed as primary modes for RDS treatment. Results are consistent and offer additional support to a previous nonrandomized observation using NSIPPV and BiPAP as primary modes in the treatment of RDS.[13] In our series, we also found a low incidence of failure (18 of 124 newborns, 15%) and a brief time of respiratory support (median for NSIPPV 89 hours; for BiPAP 87 hours). Moreover, no correlations were found between failure occurrences and GA subgroups.

Low failure in NIV support can be also explained on the basis of perinatal treatments, such as prenatal glucocorticoid prophylaxis (85% to 90% for our population), known to be effective on lung immaturity, and improvements in delivery room management such as SLI and early NCPAP. Recent observations reported an improved postnatal adaptation, in terms of lung and cardiovascular function, in SLI-treated infants and animals.[29,30] Another explanation can be the early NCPAP support in the delivery room, which is known to be beneficial for lung outcome.[2,23–28]

Although the current study shows that both methods of NIV (SIPPV and BiPAP) are feasible and probably equally effective, it does not answer the question whether NIV is better than NCPAP as primary treatment of RDS. Several authors in smaller study populations (NIPPV or BiPAP versus NCPAP) and a meta-analysis reported less need of MV, less risk of intubation in the first 72 hours from birth, and reduction of hospitalization duration and O_2 dependency.[7,10,31–33] However, Kirpalani et al, in a recent large multicenter trial, showed no significant differences in terms of mortality or BPD occurrence between NCPAP and NIV strategies, used both as first intention or in the weaning phase, but without a specific protocol for NIV (devices, modalities, synchronization).[11] Finally, Roberts et al suggested that NIPPV (synchronized or nonsynchronized) might be advantageous over NCPAP as primary support for reduction of

TABLE 3 Characteristics, Timing, and Causes of Failure of Preterm Infants Who Failed on NIV

	NSIPPV (*n* = 10)	BiPAP (*n* = 8)	*P*
BW, g	1000 ± 310	980 ± 268	.92
GA, wks	28 ± 1	28 ± 1	.93
GA ≤26 wks/total GA subgroup	2/9	2/9	1.00
GA >26 and ≤29 wks/total GA subgroup	7/33	4/32	.54
GA >29 wks/total GA subgroup	1/20	2/21	.96
Apgar score at 1 min	6 ± 1	6 ± 1	1.00
Apgar score at 5 min	8 ± 1	8 ± 1	1.00
Prenatal steroids completed course	7	6	.77
Timing of failure (median, 25°-75° centile), h	36 (17–72)	34 (19–65)	.83
Early-onset sepsis	5	3	.96
Hypoxemia	3	3	.87
Hypercapnia and hypoxemia	2	4	.32
Persistent pulmonary hypertension of the newborn	5	4	1.00
PNX	2	1	1.00
PDA	1	0	1.00
NEC	0	2	.47

Data are presented as the mean ± SD, *n*, or median (25th to 75th centile).

intubation, although there is no clear advantage.[12]

On the basis of the present findings, bearing in mind that NIV strategies can act through different modalities, further investigations evaluating their effectiveness in RDS treatment are justified.[34] Indeed, NSIPPV uses a conventional synchronized modality of intermittent positive pressure ventilation, delivered through a nasal interface, whereas BiPAP uses a nonsynchronized ventilation that provides alternately 2 different CPAP levels without intermittent peak of inspiratory pressure, in which newborns can breathe spontaneously, creating 2 different FRCs. Both methods have theoretical benefits. In particular, (1) NSIPPV through intermittent increase in pressure enhances tidal volume (V_T), minute ventilation, and MAP, resulting in better alveolar recruitment and gas exchange[9,12,35]; (2) BiPAP, by using a much longer $time_{high}$, permits a complete respiratory cycle (inspiration and expiration) on the higher CPAP level, creating 2 different FRCs; increases MAP; and FRC switching generates a V_T with better gas exchange.[7,36] Additional common NIV advantages, due to pressure changes, consist in the stimulation of spontaneous breathing that reduces failure risk due to apneas.[37] Another issue deserving further consideration concerns NIV settings. On the one hand, several authors highlight the need for strict protocols and guidelines[6–38]; on the other hand, there is still no consensus, since conflicting results have been reported in terms of variability of airway pressure from the set pressure, increase in V_T and minute ventilation, and the drop in work of breathing.[39–43] Therefore, further studies are needed to evaluate the transmission of setting pressures to the lower airways in an open system with large and variable leakage and improve NIV synchronization systems with infant spontaneous breathing. However, we found no difference in effectiveness between nasal-flow synchronized (NSIPPV) and nonsynchronized (BiPAP) strategies.

Data on prophylactic/early surfactant administration available at the time of patient recruitment were still controversial and under debate. Therefore, in infants ≤26 wGA, we chose prophylactic surfactant administration (ie, within 2 hours from birth, after stabilization on NCPAP) for the higher risk of failure,[23] whereas a selective therapeutic strategy was planned for those >26 wGA.[44] Currently, prophylactic approaches do not seem to be justified, and further investigations to clarify the efficacy of early NIV with the best timing for surfactant administration, especially in extremely low birth weight infants, are eagerly awaited.[45] We did not find any differences between groups in the need for surfactant single/multiple doses.

In the present series, we found no statistically significant differences in secondary outcomes between the 2 NIV devices. Of course, the small number of infants eligible for statistical analysis of secondary outcomes does not allow us to draw definite conclusions. In this respect, we observed a moderate/severe BPD incidence, comparable to that of previous studies.[38,46] The low incidence of PNX, NEC, or bowel perforations suggests that NIV techniques could be considered reasonably safe for these infants.

Last but not least, successful NIV management requires a high quality of neonatal care. High-risk infants require experienced nurses for the best cleaning of the upper airways, nasal cannula positioning, and maintaining the containment position of the newborns. These precautions are implemented to ensure effective airflow, maintaining adequate pressure from the nostrils to the distal airways, to increase comfort of the newborns and prevent trauma to the nostrils.[47]

CONCLUSIONS

The present data show that both NSIPPV and BiPAP, used as primary respiratory support in the treatment of RDS of VLBW infants, are feasible and equally effective. These results prompt further RCT investigations to evaluate the effectiveness of different NIV strategies on long-term outcomes.

ACKNOWLEDGMENTS

This study is part of the Italia Olanda PhD International Program, under the auspices of the Italian Society of Neonatology and of the Neonatal Clinical Biochemistry Research Group, and was partially supported by grants to DG from I Colori della Vita Foundation, Italy.

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: Prof Zimmermann has received payments from Chiesi BV and AbbVie BV for lectures in industry sponsored symposia or workshop, indirectly related to the topic of this paper; the other authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: Prof Zimmermann has received payments from Chiesi BV and AbbVie BV for lectures in industry-sponsored symposia or workshops, indirectly related to the topic of this paper; the other authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Crowley P, Chalmers I, Keirse MJNC. The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. *Br J Obstet Gynaecol*. 1990;97(1):11–25
2. Committee on Fetus and Newborn; American Academy of Pediatrics. Respiratory support in preterm infants at birth. *Pediatrics*. 2014;133(1):171–174
3. Stevens TP, Harrington EW, Blennow M, Soll RF. Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. *Cochrane Database Syst Rev*. 2007;17(4):CD003063
4. Sweet DG, Carnielli V, Greisen G, et al; European Association of Perinatal Medicine. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants - 2010 update. *Neonatology*. 2010;97(4):402–417
5. de Winter JP, de Vries MA, Zimmermann LJ. Clinical practice: noninvasive respiratory support in newborns. *Eur J Pediatr*. 2010;169(7):777–782
6. Bhandari V. Nasal intermittent positive pressure ventilation in the newborn: review of literature and evidence-based guidelines. *J Perinatol*. 2010;30(8): 505–512
7. Lista G, Castoldi F, Fontana P, et al. Nasal continuous positive airway pressure (CPAP) versus bi-level nasal CPAP in preterm babies with respiratory distress syndrome: a randomised control trial. *Arch Dis Child Fetal Neonatal Ed*. 2010; 95(2):F85–F89
8. DiBlasi RM. Neonatal noninvasive ventilation techniques: do we really need to intubate? *Respir Care*. 2011;56(9): 1273–1294, discussion 1295–1297
9. Mahmoud RA, Roehr CC, Schmalisch G. Current methods of non-invasive ventilatory support for neonates. *Paediatr Respir Rev*. 2011;12(3):196–205
10. Meneses J, Bhandari V, Alves JG. Nasal intermittent positive-pressure ventilation vs nasal continuous positive airway pressure for preterm infants with respiratory distress syndrome: a systematic review and meta-analysis. *Arch Pediatr Adolesc Med*. 2012;166(4): 372–376
11. Kirpalani H, Millar D, Lemyre B, Yoder BA, Chiu A, Roberts RS; NIPPV Study Group. A trial comparing noninvasive ventilation strategies in preterm infants. *N Engl J Med*. 2013;369(7):611–620
12. Roberts CT, Davis PG, Owen LS. Neonatal non-invasive respiratory support: synchronised NIPPV, non-synchronised NIPPV or bi-level CPAP: what is the evidence in 2013? *Neonatology*. 2013; 104(3):203–209
13. Ricotti A, Salvo V, Zimmermann LJI, et al. N-SIPPV versus bi-level N-CPAP for early treatment of respiratory distress syndrome in preterm infants. *J Matern Fetal Neonatal Med*. 2013;26(13): 1346–1351
14. Lista G, Fontana P, Castoldi F, Cavigioli F, Dani C. Does sustained lung inflation at birth improve outcome of preterm infants at risk for respiratory distress syndrome? *Neonatology*. 2011;99(1): 45–50
15. Perlman JM, Wyllie J, Kattwinkel J, et al; Neonatal Resuscitation Chapter Collaborators. Neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. *Pediatrics*. 2010;126(5). Available at: www.pediatrics.org/cgi/content/full/126/5/e1319
16. te Pas AB, Walther FJ. A randomized, controlled trial of delivery-room respiratory management in very preterm infants. *Pediatrics*. 2007;120(2): 322–329
17. Salvo V, Zimmermann LJ, Gavilanes AW, et al. First intention high-frequency oscillatory and conventional mechanical ventilation in premature infants without antenatal glucocorticoid prophylaxis. *Pediatr Crit Care Med*. 2012;13(1):72–79
18. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. *Ann Surg*. 1978;187(1): 1–7
19. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med*. 2001;163(7):1723–1729
20. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr*. 1978;92(4):529–534
21. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Arch Ophthalmol*. 2005;123(7):991–999
22. O'Brien RG, Muller KE. *Applied Analysis of Variance in Behavioral Science*. New York, NY: Marcel Dekker; 1983:297–344
23. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB; COIN Trial Investigators. Nasal CPAP or intubation at birth for very preterm infants. *N Engl J Med*. 2008;358(7):700–708
24. Finer NN, Carlo WA, Walsh MC, et al; SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. *N Engl J Med*. 2010;362(21):1970–1979
25. Sandri F, Plavka R, Ancora G, et al; CURPAP Study Group. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. *Pediatrics*. 2010;125(6). Available at: www.pediatrics.org/cgi/content/full/125/6/e1402
26. Dunn MS, Kaempf J, de Klerk A, et al; Vermont Oxford Network DRM Study Group. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics*. 2011;128(5). Available at: www.pediatrics.org/cgi/content/full/128/5/e1069
27. Tapia JL, Urzua S, Bancalari A, et al; South American Neocosur Network. Randomized trial of early bubble continuous positive airway pressure for very low birth weight infants. *J Pediatr*. 2012;161(1):75–, e1
28. Carlo WA. Gentle ventilation: the new evidence from the SUPPORT, COIN, VON, CURPAP, Colombian Network, and Neocosur Network trials. *Early Hum Dev*. 2012;88(suppl 2):S81–S83
29. te Pas AB, Siew M, Wallace MJ, et al. Establishing functional residual capacity at birth: the effect of sustained inflation and positive end-expiratory pressure in a preterm rabbit model. *Pediatr Res*. 2009;65(5):537–541

30. te Pas AB, Spaans VM, Rijken M, Morley CJ, Walther FJ. Early nasal continuous positive airway pressure and low threshold for intubation in very preterm infants. *Acta Paediatr*. 2008;97(8): 1049–1054

31. Kugelman A, Feferkorn I, Riskin A, Chistyakov I, Kaufman B, Bader D. Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure for respiratory distress syndrome: a randomized, controlled, prospective study. *J Pediatr*. 2007;150(5): 521–526, e1

32. Sai Sunil Kishore M, Dutta S, Kumar P. Early nasal intermittent positive pressure ventilation versus continuous positive airway pressure for respiratory distress syndrome. *Acta Paediatr*. 2009; 98(9):1412–1415

33. Meneses J, Bhandari V, Alves JG, Herrmann D. Noninvasive ventilation for respiratory distress syndrome: a randomized controlled trial. *Pediatrics*. 2011;127(2):300–307

34. DeMauro SB, Millar D, Kirpalani H. Noninvasive respiratory support for neonates. *Curr Opin Pediatr*. 2014;26(2): 157–162

35. Bancalari E, Claure N. Non-invasive ventilation of the preterm infant. *Early Hum Dev*. 2008;84(12):815–819

36. Migliori C, Motta M, Angeli A, Chirico G. Nasal bilevel vs. continuous positive airway pressure in preterm infants. *Pediatr Pulmonol*. 2005;40(5):426–430

37. Lemyre B, Davis PG, de Paoli AG. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for apnea of prematurity. *Cochrane Database Syst Rev*. 2002;1(1):CD002272

38. Bhandari V. The potential of non-invasive ventilation to decrease BPD. *Semin Perinatol*. 2013;37(2):108–114

39. Owen LS, Morley CJ, Dawson JA, Davis PG. Effects of non-synchronised nasal intermittent positive pressure ventilation on spontaneous breathing in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(6):F422–F428

40. Owen LS, Morley CJ, Davis PG. Pressure variation during ventilator generated nasal intermittent positive pressure ventilation in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2010;95(5): F359–F364

41. Aghai ZH, Saslow JG, Nakhla T, et al. Synchronized nasal intermittent positive pressure ventilation (SNIPPV) decreases work of breathing (WOB) in premature infants with respiratory distress syndrome (RDS) compared to nasal continuous positive airway pressure (NCPAP). *Pediatr Pulmonol*. 2006;41(9): 875–881

42. Ali N, Claure N, Alegria X, D'Ugard C, Organero R, Bancalari E. Effects of non-invasive pressure support ventilation (NI-PSV) on ventilation and respiratory effort in very low birth weight infants. *Pediatr Pulmonol*. 2007;42(8):704–710

43. Chang HY, Claure N, D'ugard C, Torres J, Nwajei P, Bancalari E. Effects of synchronization during nasal ventilation in clinically stable preterm infants. *Pediatr Res*. 2011;69(1):84–89

44. Bohlin K. RDS—CPAP or surfactant or both. *Acta Paediatr Suppl*. 2012;101(464): 24–28

45. Polin RA, Carlo WA; Committee on Fetus and Newborn; American Academy of Pediatrics. Surfactant replacement therapy for preterm and term neonates with respiratory distress. *Pediatrics*. 2014;133(1):156–163

46. Verder H, Bohlin K, Kamper J, Lindwall R, Jonsson B. Nasal CPAP and surfactant for treatment of respiratory distress syndrome and prevention of bronchopulmonary dysplasia. *Acta Paediatr*. 2009;98(9):1400–1408

47. Askin DF. Noninvasive ventilation in the neonate. *J Perinat Neonatal Nurs*. 2007; 21(4):349–358, quiz 359–360

Noninvasive Ventilation Strategies for Early Treatment of RDS in Preterm Infants: An RCT

Vincenzo Salvo, Gianluca Lista, Enrica Lupo, Alberto Ricotti, Luc J.I. Zimmermann, Antonio W.D. Gavilanes, Ignazio Barberi, Micaela Colivicchi, Francesca Temporini and Diego Gazzolo

Pediatrics 2015;135;444
DOI: 10.1542/peds.2014-0895 originally published online February 9, 2015;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Noninvasive Ventilation Strategies for Early Treatment of RDS in Preterm Infants: An RCT

Vincenzo Salvo, Gianluca Lista, Enrica Lupo, Alberto Ricotti, Luc J.I. Zimmermann, Antonio W.D. Gavilanes, Ignazio Barberi, Micaela Colivicchi, Francesca Temporini and Diego Gazzolo

Pediatrics 2015;135;444
DOI: 10.1542/peds.2014-0895 originally published online February 9, 2015;