SNIPPV vs. NIPPV: DOES SYNCHRONIZATION MATTER?

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Abstract

Background—Use of nasal intermittent positive pressure ventilation (NIPPV) in the neonatal intensive care unit (NICU) has shown promise with better clinical outcomes in premature neonates. It is not known if synchronization makes a significant clinical impact when using this technique.

Objective—To compare clinical outcomes of premature infants on synchronized NIPPV (SNIPPV) vs. NIPPV in the NICU.

Design/Methods—Retrospective data were obtained (1/04 to 12/09) of infants who received NIPPV anytime in the NICU. SNIPPV (Infant Star with StarSync) was utilized from 2004–06, while NIPPV (Bear Cub) was used from 2007–09. BPD was defined using the NIH consensus definition. Unadjusted associations between potential risk factors and BPD/death were assessed using the chi-square or Wilcoxon Rank Sum test. Adjusted analyses were performed using generalized linear mixed models, taking into account correlation among infants of multiple gestation.

Results—There was no significant difference in the mean gestational age and birth weight in the 2 groups: SNIPPV (n=172; 27.0w; 1016g), NIPPV (n=238; 27.7w; 1117g). There were no significant differences in maternal demographics, use of antenatal steroids, gender, multiple births, SGA, or Apgar scores in the 2 groups. More infants in the NIPPV group were given resuscitation in the delivery room (SNIPPV vs. NIPPV: 44.2% vs. 63%, p<0.001). Surfactant use (84.4% vs. 70.2%; p<0.001) was significantly higher in the SNIPPV group. There were no differences in the rate of PDA, IVH, PVL, ROP, and NEC in the 2 groups. After adjusting for the significant variables, use of NIPPV vs. SNIPPV (OR 0.74; 95%CI: 0.42, 1.30) was not associated with BPD/death.

Conclusions—These data suggest that use of SNIPPV vs. NIPPV is not significantly associated with a differential impact on clinical outcomes.
INTRODUCTION

Nasal intermittent positive pressure ventilation (NIPPV) is a form of non-invasive ventilatory assistance using a nasal interface to provide respiratory support.\(^1\) NIPPV has been shown to be superior to nasal continuous positive airway pressure (NCPAP) or conventional mechanical ventilation, as a method of reducing the incidence of extubation failure and pulmonary morbidities including bronchopulmonary dysplasia (BPD).\(^1\) NIPPV may be synchronized (SNIPPV) or non-synchronized to the infants breathing efforts. Many randomized controlled trials (RCT) have been conducted proving the efficacy of SNIPPV/NIPPV in keeping the infant extubated and/or decreasing BPD compared with other modes of respiratory support.\(^2\)–\(^8\)

The effectiveness of SNIPPV could be due to the decrease in the thoraco-abdominal motion asynchrony and flow resistance through nasal prongs, with improved stability of chest wall and pulmonary mechanics.\(^9\) Addition of peak inspiratory pressure (PIP) above positive end expiratory pressure (PEEP) by using SNIPPV leads to increased intermittent distending pressure above PEEP, with increased flow delivery in the upper airway.\(^2\) Moretti et al reported that application of SNIPPV was associated with increased tidal and minute volumes when compared with NCPAP in the same infant.\(^10\) It is also possible that SNIPPV recruits collapsed alveoli and increases functional residual capacity. Aghai et al have reported that infants receiving SNIPPV have decreased work of breathing.\(^11\)

There is limited information available comparing the effectiveness of SNIPPV vs. NIPPV. The goal of the present study was to compare the clinical outcomes of infants who were managed with SNIPPV versus those infants who were on NIPPV anytime during their stay in the Newborn Special Care Unit (NBSCU) at Yale.

METHODS

At Yale, prior to 2007, NIPPV was delivered through a ventilator which synchronized breaths with infant’s respiratory efforts and was termed SNIPPV. SNIPPV was delivered using the Infant Star ventilator with StarSync (Infrasonics Inc.), and synchronization with infant’s respiratory efforts was achieved utilizing the Graseby capsule. NIPPV replaced SNIPPV, as the Infant Star ventilator was phased out of production in the United States. From 2007, NIPPV has been utilized using the Bear Cub 750 psv (CareFusion Inc., San Diego, CA) ventilator.

Clinical retrospective data were collected on infants (n=410) admitted to the NBSCU at Yale-New Haven Children’s Hospital, New Haven, CT, USA from Jan 1st, 2004 to Dec 31st, 2009. The criteria for inclusion were all infants who were admitted to NBSCU and received SNIPPV/NIPPV anytime during their stay. BPD was defined using the National Institutes of
Health (NIH) consensus definition. Data collection was approved by the Yale institutional review board (Human Investigation Committee).

Clinical Data Collection

The maternal and neonatal characteristics have been shown in Supplemental Table 1. Antenatal steroid treatment was defined as at least a 12h interval between maternal dosing and subsequent delivery of the infant. Resuscitation after birth was defined as being given bag and mask ventilation and/or intubation and/or chest compression and/or drugs. Patent ductus arteriosus (PDA) was documented by echocardiography. Intraventricular hemorrhage (IVH) was determined according to Papile’s classification of blood in the germinal matrix or ventricular system with or without ventricular dilatation and parenchymal extension. Periventricular leukomalacia (PVL) was defined as cerebral ultrasound findings of increased echogenicity and cystic lesions in the periventricular white matter. Sepsis was diagnosed by a positive blood culture. Necrotizing enterocolitis (NEC) was defined as ≥ stage 2 as per modified Bell’s criteria. Retinopathy of prematurity (ROP) was defined as per the international classification.

Infants were classified into two different groups, based on the type of respiratory support they received, SNIPPV (2004 to 2006) and NIPPV (2007 to 2009). The main outcome of the study was incidence of BPD/death in the groups.

Statistical analyses

Maternal, perinatal and neonatal characteristics of infants in the two groups of respiratory support (SNIPPV and NIPPV), as well as unadjusted associations between potential risk factors and BPD/death were compared using chi-square or Wilcoxon Rank Sum test. Adjusted analyses for the probability of having BPD/death were performed using generalized linear mixed models, taking into account correlation among infants of multiple gestation. A p-value of ≤0.05 was considered statistically significant. Data were analyzed using SAS 9.2 (Cary, NC).

RESULTS

Out of the total 410 infants included in the study, 172 were classified into SNIPPV group and 238 into NIPPV group. As already mentioned, the classification was based on the type of NIPPV, synchronized (2004–2006) or non-synchronized (2007–2009).

Supplemental Table 1 lists the demographic and clinical characteristics of infants in both groups. There was no significant difference in the mean gestational age (GA) and birth weight (BW) between the two groups. There was also no difference in gender, maternal age, antenatal steroids, small for gestational age (SGA), and Apgar scores in the two groups.

More infants in the NIPPV group were given resuscitation (63 vs. 44.2%, p < 0.001) while more infants in SNIPPV group needed surfactant administration (84.4% vs. 70.2%, p < 0.001). There was no significant difference in the duration of ETT ventilation or SNIPPV/NIPPV in infants in the two groups, but infants in NIPPV were exposed to NCPAP for slightly longer duration of time (p<0.02) (Table 1).
No differences were noted in the rate of sepsis, PDA, IVH, PVL, ROP, and NEC in the two groups (Table 1).

There were eight deaths in the SNIPPV group and nine in the NIPPV group. There were no instances of intestinal perforation in the SNIPPV group; however, there were twelve instances of intestinal perforation in the NIPPV group out of which ten were spontaneous intestinal perforation (SIP). Details have been provided in Table 2.

Based on unadjusted analyses, BPD/death was significantly increased in the SNIPPV group (63.4% vs. 51.6%, p<0.02). After adjusting for variables such as BW, gender, race, given resuscitation, sepsis, surfactant administration, and days on TPN (Table 3), use of NIPPV, as compared with SNIPPV, was not associated with increased probability of BPD/death (OR 0.74; 95% CI 0.42, 1.30).

DISCUSSION

With the increased interest in nasal ventilation as the primary mode of respiratory support in premature infants to reduce extubation failure and/or BPD, it is important to know if synchronization has any added benefit. Studies have been conducted and are ongoing comparing SNIPPV/NIPPV to other modes of ventilation, but no study has reported on detailed clinical outcomes, comparing SNIPPV to NIPPV.

Moretti et al conducted a study in which infants weighing <1251g with respiratory distress syndrome (RDS) requiring mechanical ventilation at 48h of age were extubated randomly to SNIPPV or NCPAP, once the criteria were met. Infants in SNIPPV group had a higher incidence of successful extubation compared to those in NCPAP group (90 vs. 61%, p=0.005).6 In our previous studies, it has been shown that SNIPPV decreased the duration of intubation and the need for supplemental oxygen as compared to mechanical ventilation in premature infants with RDS.17 In a subsequent RCT, comparing SNIPPV to ETT ventilation, it was shown that infants in SNIPPV group had fewer outcomes of BPD/death compared to those in ETT group (20 vs. 52%, p=0.03).4

The long term outcomes of premature infants managed on SNIPPV were comparable to those of infants managed on conventional ventilation. In a RCT done using SNIPPV, no differences were reported in the Mental or Psychomotor Developmental Index scores on follow up between the infants managed with SNIPPV or continued on conventional mechanical ventilation (CMV).4 In another large retrospective study done to evaluate use of SNIPPV in infants ≤250g, it was observed that, infants who received SNIPPV (compared with those who received NCPAP) in the BW category 500–750g were significantly less likely to have the long term outcomes of BPD, BPD/death, neurodevelopmental impairment and neurodevelopmental impairment/death. It is again worth mentioning that no study has been done reporting on long term outcomes on infants managed with SNIPPV vs. NIPPV.18

Studies done comparing NIPPV to other modes of ventilation have also yielded similar outcomes. Kugelman et al showed that infants treated initially with NIPPV needed less ETT ventilation (25 vs. 49%, p< 0.05), had decreased incidence of BPD (2 vs. 17%, p< 0.05), compared to infants treated initially with NCPAP.7 Similarly, in another RCT comparing
infants with RDS receiving NIPPV within six hours, to those receiving NCPAP, it was shown that infants on NIPPV had lower rates of extubation failure, but had similar rates of BPD. Khorana et al. conducted a RCT comparing NIPPV and NCPAP, in which premature infants were randomized to either of the two groups after extubation. The primary outcome of reintubation rates and other measured outcomes such as apnea, abdominal distension, sepsis, and NEC were not significantly different in both groups. However, the two groups of NIPPV and NCPAP were not well matched: infants in NIPPV group had lower mean BW, higher rates of RDS and antenatal steroid use. Also, after extubation, in the NIPPV group, the PIP was not increased by 4 cm H₂O above that required during manual ventilation, as has been recommended.

Mala Kumar et al. conducted a RCT recently, comparing NIPPV to ‘oxygen by head box’ and found that NIPPV significantly reduced extubation failure. The timing of initiation of SNIPPV/NIPPV is also a key factor in the outcome of BPD/death. In a recent study conducted by our group, it was observed that infants who were on NIPPV for most of the time in the first week of life compared to being on ETT, had a decreased incidence of BPD/death.

There have been 2 reports, comparing SNIPPV to NIPPV, evaluating short-term effects. Recently, Chang et al. studied the effects of synchronization during nasal ventilation comparing nasal intermittent mandatory ventilation (NIMV), synchronized NIMV (SNIMV) and NCPAP in a randomized manner, each for 1h. They concluded that synchronized nasal ventilation reduced breathing effort and resulted in better infant–ventilator interaction than non-synchronized nasal ventilation. Owen et al studied effects of NIPPV on spontaneous breathing and proposed that synchronization of NIPPV pressure peaks with spontaneous inspirations may increase the benefits of NIPPV.

Our present study compares SNIPPV vs. NIPPV by examining the clinical characteristics of infants and the clinical outcome of BPD/death. Neither mode of nasal ventilation was found to be superior with respect to these outcomes.

The most serious complication associated with the use of SNIPPV/NIPPV in neonates has been gastrointestinal perforation. Use of SNIPPV has been associated with a “reassuring absence of gastrointestinal side effects”. In the present study, the rate of intestinal perforations was higher during the NIPPV study period. However, these perforations occurred with the infants being on different modes of ventilation. Hence, we were unable to specifically associate gastrointestinal perforations with SNIPPV or NIPPV use, as had been reported in the pre-surfactant era publication. The study by Sai Sunil Kishore et al. noted a slight increase in abdominal distension in the NIPPV group vs. CMV, but this difference was not statistically significant. Furthermore, there was no difference in the tolerance of feeds. In our study, days on TPN were lower in a trend favoring NIPPV. Thus, it would appear that the suggested guidelines on the technique of providing (S)NIPPV are safe.

The major limitation to our study is its retrospective nature. However, the strengths of the study include the large sample size, detailed evaluation of clinical outcomes based on mode of respiratory support, and the use of NIH consensus definition for BPD.
CONCLUSION

Use of SNIPPV relative to NIPPV did not show a significantly different impact on clinical outcomes in premature infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

| Abbreviation (3-letter) | Full Form |
|------------------------|-----------|
| BW                    | Birth Weight |
| BPD                   | Bronchopulmonary dysplasia |
| CMV                   | Conventional mechanical ventilation |
| ETT                   | Endotracheal tube ventilation |
| GA                    | Gestational age |
| IVH                   | Intraventricular hemorrhage |
| NBSCU                 | Newborn special care unit |
| NCPAP                 | Nasal continuous positive airway pressure |
| NEC                   | Necrotizing enterocolitis |
| NICU                  | Neonatal intensive care unit |
| NIPPV                 | Nasal intermittent positive airway pressure |
| PDA                   | Patent ductus arteriosus |
| PEEP                  | Positive end expiratory pressure |
| PIH                   | Pregnancy induced hypertension |
| PIP                   | Peak inspiratory pressure |
| PVL                   | Periventricular leukomalacia |
| RCT                   | Randomized controlled trial |
| RDS                   | Respiratory distress syndrome |
| ROP                   | Retinopathy of prematurity |
| SGA                   | Small for gestational age |
| SIP                   | Spontaneous intestinal perforations |
SNIPPV  Synchronized nasal intermittent positive pressure ventilation
TPN  Total parenteral nutrition

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Table 1

Neonatal outcomes in the two groups.

| CHARACTERISTIC                | SNIPPV (n=172) | NIPPV (n=238) | p-value |
|-------------------------------|----------------|---------------|---------|
| Days on ETT IPPV             | Median, (range) | 8.5 (0 – 141) | 10.5 (0 – 141) | 0.67 |
| Days on SNIPPV/NIPPV         | Median, (range) | 7.5 (1 – 49)  | 7 (1 – 42)   | 0.36 |
| Days on NCPAP                | Median, (range) | 7.5 (0 – 36)  | 4 (0 – 97)   | 0.02 |
| Sepsis (early- or late-onset)| N,%            | 63 (36.6)     | 73 (30.7)    | 0.21 |
| PDA                           | N,%            | 35 (23.6)     | 41 (17.2)    | 0.42 |
| IVH                           | N,%            | 31 (18)       | 46 (19.3)    | 0.74 |
| PVL                           | N,%            | 6 (3.5)       | 4 (1.7)      | 0.33 |
| ROP                           | N,%            | 72 (41.9)     | 99 (41.6)    | 0.95 |
| NEC                           | N,%            | 23 (13.4)     | 27 (11.3)    | 0.54 |
| Days on TPN                  | Median, (range) | 24 (0 – 120)  | 21 (0 – 199) | 0.05 |
| Length of stay               | Median, (range) | 70 (5 – 207)  | 74 (4 – 330) | 0.35 |

ETT/IPPV: endotracheal tube intermittent positive pressure ventilation; SNIPPV/NIPPV: synchronized/nasal intermittent positive pressure ventilation; NCPAP: nasal continuous positive airway pressure; PDA: patent ductus arteriosus; IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; ROP: retinopathy of prematurity; NEC: necrotizing enterocolitis; TPN: total parenteral nutrition.
### Table 2

Intestinal perforations in the NIPPV group (2007–2009).

| Case Number | GA  | BW  | Diagnosis                | Mode of Respiratory Support at time of Perforation | Comments                                                                 |
|-------------|-----|-----|--------------------------|--------------------------------------------------|--------------------------------------------------------------------------|
| 1           | 24’6| 800 | SIP on DOL 4             | NCPAP                                            | On NCPAP from DOL 1 to 4                                                 |
| 2#          | 25’3| 895 | SIP on DOL 7             | NCPAP                                            | Given ibuprofen on DOL 3 to 4 for PDA closure. Intubated at referring hospital prior to transfer to Yale for Rx of bowel perforation |
| 3           | 23’6| 520 | NEC on DOL 50            | ETT                                              | Given dexamethasone on DOL 47 to 50. Extubated to NIPPV on DOL 74         |
| 4*          | 24’2| 730 | SIP on DOL 6             | ETT                                              | Extubated to NIPPV after 6 weeks of life                                  |
| 5*          | 24’2| 700 | SIP on DOL 6             | ETT                                              | Extubated to NIPPV on DOL 10                                             |
| 6           | 30’2| 1080| SIP on DOL 8             | NCPAP                                            | Initially on NCPAP to NIPPV to intubation on DOL 3. Extubated on DOL 7.  |
| 7           | 24’6| 810 | Gastric perforation on DOL 31 | NIPPV                                      | Given indomethacin on DOL 19 to 20 for PDA closure. Extubated to NIPPV on DOL 23. Died on DOL 54 due to multiorgan failure/sepsis |
| 8           | 25’3| 950 | SIP on DOL 6             | ETT                                              | Extubated to NIPPV on DOL 28                                             |
| 9           | 24’1| 630 | SIP on DOL 8             | ETT                                              | Intubated for first 3 weeks of life                                      |
| 10*         | 25’4| 910 | SIP on DOL 6             | NIPPV                                            | Extubated to NIPPV on DOL 5                                              |
| 11*         | 25’4| 910 | SIP on DOL 6             | ETT                                              | Extubated to NIPPV on DOL 22                                             |
| 12          | 25’0| 790 | SIP on DOL 7             | ETT                                              | Extubated to NIPPV on DOL 27                                             |

*Twins; GA: gestational age (weeks); BW: birth weight (grams); DOL: day of life; SIP: spontaneous intestinal perforation (ileal); NCPAP: nasal continuous airway pressure; PDA: patent ductus arteriosus; ETT: endotracheal tube; NIPPV: nasal intermittent positive pressure ventilation.

All infants (except #) received indomethacin for intraventricular hemorrhage prophylaxis for 3 days, given q 24h, as per nursery protocol.
Table 3
Multivariate analysis of NIPPV vs. SNIPPV predicting BPD/death.

| CHARACTERISTIC                      | OR (95% CI)       | p-value |
|-------------------------------------|-------------------|---------|
| Ventilation                        |                   |         |
| NIPPV                               | 0.74 (0.42, 1.3)  | 0.29    |
| SNIPPV                              | Reference         |         |
| Birth weight (g)                    | 0.997 (0.996, 0.998) | <0.001 |
| Male Gender                         | 1.64 (0.94, 2.86) | 0.08    |
| Race                                |                   |         |
| White                               | 1.07 (0.53, 2.17) | 0.30    |
| Black                               | 0.66 (0.30, 1.44) |         |
| Hispanic                            | Reference         |         |
| Given resuscitation                 | 1.32 (0.75, 2.34) | 0.33    |
| Sepsis                              | 1.26 (0.68, 2.35) | 0.47    |
| Surfactant (rescue) administration  | 3.91 (1.93, 7.94) | <0.001  |
| Total parenteral nutrition days     | 1.04 (1.03, 1.06) | <0.001  |

SNIPPV/NIPPV: synchronized/nasal intermittent positive pressure ventilation; BPD: bronchopulmonary dysplasia.