REVIEW ARTICLE

Nasal Intermittent Positive-Pressure Ventilation vs Nasal Continuous Positive Airway Pressure for Preterm Infants With Respiratory Distress Syndrome

A Systematic Review and Meta-analysis

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Objective: To determine among preterm infants with respiratory distress syndrome whether the use of early nasal intermittent positive-pressure ventilation (NIPPV) vs nasal continuous positive airway pressure (NCPAP) decreases the need for invasive ventilation within the first 72 hours of life.

Data Sources: MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, and clinicaltrials .gov were searched, as well as abstracts from meetings of the Pediatric Academic Societies.

Study Selection: Randomized controlled trials involving infants with respiratory distress syndrome who received NIPPV vs NCPAP.

Data Extraction: Data were extracted on the use of NIPPV vs NCPAP. Also extracted were data on the need for invasive ventilation within the first 72 hours of life and the incidences of bronchopulmonary dysplasia, pneumothorax, necrotizing enterocolitis, and intraventricular hemorrhage, as well as the time to full feeds and the duration of hospital stay.

Data Synthesis: Three trials were included (n=360). A significant decrease in the need for invasive ventilation was found in the NIPPV group (risk ratio, 0.60; 95% CI, 0.43-0.83). No difference between groups was found in the incidence of bronchopulmonary dysplasia (risk ratio, 0.56; 95% CI, 0.09-3.49). No differences in the other outcomes were observed between the 2 groups.

Conclusions: Among preterm infants with respiratory distress syndrome, NIPPV decreases the need for invasive ventilation within the first 72 hours of life compared with NCPAP. Trials are needed to assess whether NIPPV minimizes the occurrence of bronchopulmonary dysplasia and other comorbidities.

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THERE HAS BEEN SUBSTANTIAL interest in the use of noninvasive ventilation for preterm infants, aiming to reduce invasive mechanical ventilation and associated complications.[1] The need for mechanical ventilation, especially early in life, is a major risk factor for the complex disorder of bronchopulmonary dysplasia (BPD).[2] Nasal continuous positive airway pressure (NCPAP) is an initial respiratory support mode for many preterm infants with respiratory distress syndrome (RDS), and this has contributed to a significant decrease in the incidence of BPD at some centers.[3,4] However, some infants fail NCPAP, and a newer noninvasive strategy that uses nasal intermittent positive-pressure ventilation (NIPPV), with or without synchronization, has gained support as a mode of respiratory support for these infants.[5,6] Recent surveys have indicated that most of the neonatal intensive care units worldwide are increasingly using NIPPV.[7,8]

Studies[9-11] have shown that NIPPV compared with NCPAP reduces thoracoabdominal asynchrony, decreases the work of breathing, increases tidal volume and minute ventilation, and improves oxygen saturation. In a 2011 study, Chang et al[12] demonstrated among a small sample of infants that tidal volume and minute ventilation did not differ whether NCPAP, NIPPV, or synchronized nasal intermittent positive-pressure ventilation (SNIPPV) was used. However, significant reduction in spontaneous breathing effort and better infant-ventilator interaction were observed in the SNIPPV group. The authors pointed out some limitations of their findings. First, they documented only short-term effects of the noninvasive ventilation; second, the study groups were composed of clinically stable infants. Sicker infants with worse lung mechanics seem

to benefit more from nasal ventilatory support than stable preterm infants.

There is evidence that NIPPV compared with NCPAP reduces extubation failures and rates of apnea in preterm infants.[13,14] Trials have demonstrated that, when used as a primary mode of respiratory support in preterm infants with RDS, NIPPV is more effective than NCPAP in reducing the need for invasive ventilation within the first days of life.[15-17] Further studies are needed to evaluate the potential benefits of NIPPV on the incidence of BPD.

The objective of this systematic review was to determine among preterm infants with RDS whether the use of NIPPV vs NCPAP decreases the need for invasive ventilation within the first 72 hours of life. The effect of treatment with NIPPV vs NCPAP was also examined relative to the incidences of BPD, pneumothorax, necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH), as well as the time to full feeds and the duration of hospital stay.

METHODS

This systematic review and meta-analysis was conducted according to current standards from version 5.1.0 of the *Cochrane Handbook for Systematic Reviews of Interventions*,[18] and reporting was done following the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines.[19] The databases MEDLINE, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, and clinicaltrials.gov were searched for articles published between January 1, 1990, and April 30, 2011, with no language restriction, as well as abstracts from meetings of the Pediatric Academic Societies (2000-2011). The following Medical Subject Headings (MeSH) terms were used: *continuous positive airway pressure* [MeSH] AND *positive-pressure respiration* [MeSH] AND *respiratory distress syndrome, newborn* [MeSH], limited to randomized controlled trials (RCTs). The criteria for a trial to be included in the study were as follows: (1) trial involving preterm infants with RDS, (2) trial comparing noninvasive ventilation strategies (NIPPV and NCPAP), and (3) infants needing intubation and mechanical ventilation.

We independently reviewed the studies for eligibility and assessed trial quality according to the following Cochrane guidelines: adequate sequence generation, allocation concealment, blinding of investigators and outcome assessors, completeness of outcome data, and selective outcome reporting. Two of us (J.M. and J.G.A.) independently extracted data, and disagreements were resolved by all of us.

The primary outcome was the need for intubation and mechanical ventilation within the first 72 hours of life. Secondary outcomes were the incidences of BPD (defined as the need for supplemental oxygen, assessed at 36 weeks' postmenstrual age), NEC, pneumothorax, and IVH of any grade, as well as the time to full feeds (defined as when the infant achieved 130-150 mL/kg/d) and the duration of hospital stay.

Meta-analysis was performed using version 5.0 of *Review Manager*.[20] The binary outcomes for individual studies and pooled statistics were reported as risk ratios (RRs) (95% CIs). To assess heterogeneity, χ^2 distribution and Higgins I^2 statistics were calculated to determine the percentage of total variation across studies resulting from heterogeneity. I^2 statistics approximating 25%, 50%, and 75% were considered low, medium, and high heterogeneity, respectively. The fixed-effects models are presented, and the random-effects models were used whenever considerable heterogeneity was shown. For categorical data, the effect is expressed as the RR, and for continuous data the effect is expressed as the mean difference (95% CI).

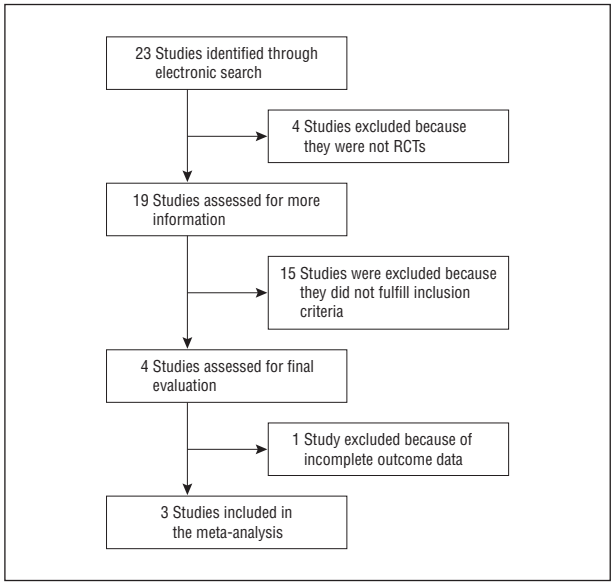

Figure 1. Flow diagram of the study selection process. RCTs indicates randomized controlled trials.

RESULTS

Twenty-three potential studies were identified, of which 4 were excluded because they were not RCTs. Nineteen trials underwent further evaluation, and 15 were excluded because they did not meet the inclusion criteria. Four trials remained; after careful evaluation, 1 was excluded because of incomplete outcome data (**Figure 1**). Characteristics of the 3 trials included in the meta-analysis (eTable 1) and their risk of bias according to the Cochrane guidelines (eTable 2) are given in the supplementary materials (http://www.archpediatrics.com).

Meta-analysis performed for the primary outcome, the need for intubation and mechanical ventilation within the first 72 hours of life, estimated a significant decrease in the need for invasive ventilation in the NIPPV group compared with the NCPAP group (RR, 0.60; 95% CI, 0.43-0.83) in the fixed-effects model (**Figure 2**). No heterogeneity was found among the 3 trials ($P = .36$, $I^2 = 1\%$). Data for the primary outcome in the subgroup of infants who received surfactant by the INSURE (intubate-surfactant-extubate) approach were reported in 2 trials[16,17] and demonstrated a tendency to a reduced risk of failure in the NIPPV group (RR, 0.72; 95% CI, 0.49-1.06), with no heterogeneity between the trials (**Figure 3**).

For the incidence of BPD, pooling of data from the 3 trials showed no difference between the treatment groups (RR, 0.56; 95% CI, 0.09-3.49) (**Figure 4**). However, significant heterogeneity was found among the trials ($P = .04$, $I^2 = 69\%$) in the fixed-effects model and the random-effects model. If we considered the denominator as the total cohort in all 3 trials, similar results were found (RR, 0.56; 95% CI, 0.09-3.61). In addition, if the composite outcome of death or BPD as the numerator was used, the results were almost the same (RR, 0.60; 95% CI, 0.25-1.45).

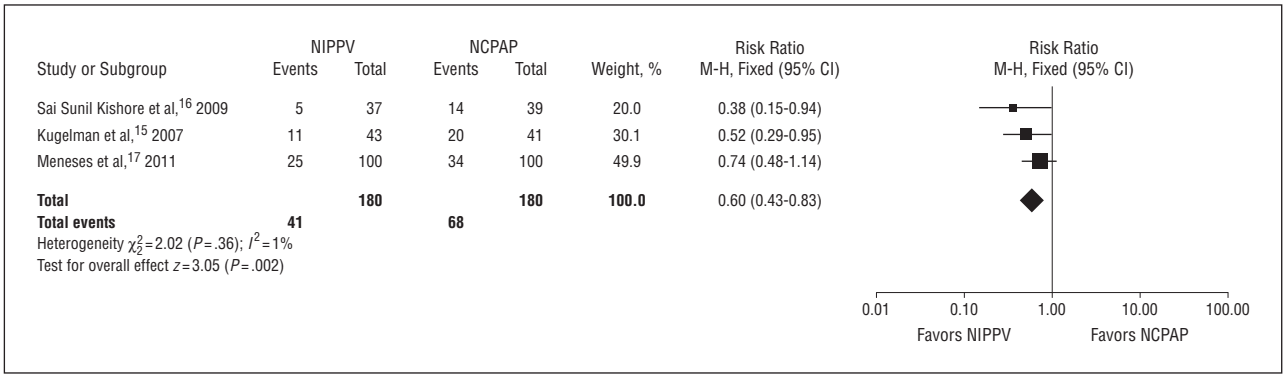

Figure 2. Need for intubation and invasive mechanical ventilation within 72 hours of life. M-H indicates Mantel-Haenszel test; NCPAP, nasal continuous positive airway pressure; and NIPPV, nasal intermittent positive-pressure ventilation.

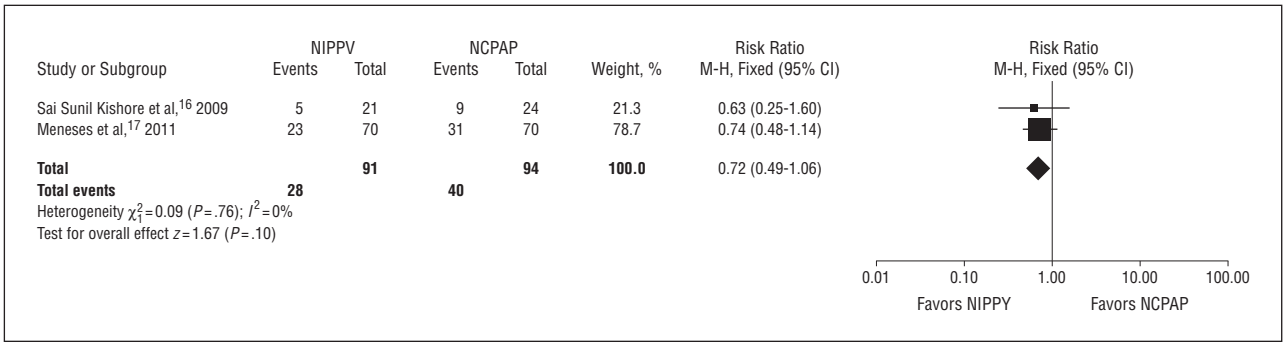

Figure 3. Need for invasive mechanical ventilation within 72 hours of life among infants who received surfactant. M-H indicates Mantel-Haenszel test; Control or NCPAP, nasal continuous positive airway pressure; and Experimental or NIPPV, nasal intermittent positive-pressure ventilation.

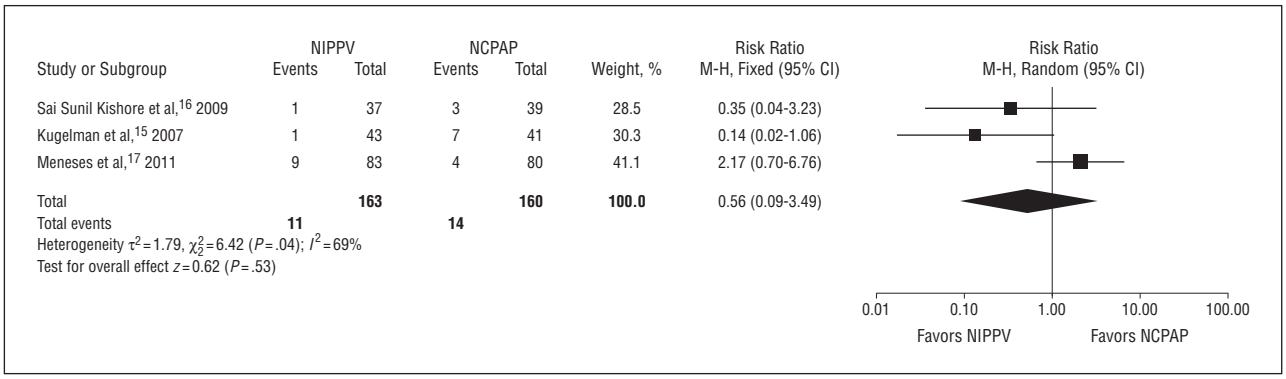

Figure 4. Incidence of bronchopulmonary dysplasia (supplemental oxygen requirement at 36 weeks' postmenstrual age). M-H indicates Mantel-Haenszel test; NCPAP, nasal continuous positive airway pressure; and NIPPV, nasal intermittent positive-pressure ventilation.

Meta-analysis of data obtained from the 3 trials estimated no significant difference in the incidence of pneumothorax (RR, 0.71; 95% CI, 0.28-1.82) between the treatment groups, with no heterogeneity among the trials (P=.49, I^2=0%) (eFigure 1). There was also no difference in the incidence of IVH (RR, 0.98; 95% CI, 0.68-1.41) (eFigure 2) or in the incidence of NEC (RR, 0.92; 95% CI, 0.41-2.07) (eFigure 3). There was no gastric perforation among 180 infants in the NIPPV group within the 3 trials. Data available from 2 trials[15,17] showed no difference in the time to full feeds in the NIPPV group compared with the NCPAP group (mean difference, –0.92; 95% CI, –2.76 to 0.93) (P=.29, I^2=11%) (eFigure 4). If the infants who died or did not reach full feeds were excluded from the analysis, results were similar to those that included the whole cohort (data not shown). There was also no difference in the duration of hospital stay between the 2 treatment groups (mean difference, –3.12; 95% CI, –11.92 to 5.68) (P=.11, I^2=55%) (eFigure 5).

COMMENT

The results of this meta-analysis involving 3 RCTs show the benefit of NIPPV in preterm infants with RDS, with a significant reduction in the need for intubation and invasive mechanical ventilation within the first 72 hours of life. There was a trend favoring NIPPV in the 2 trials with the subgroup of infants who received surfactant by the INSURE approach.[16,17] These findings suggest that NIPPV aug-

ments the beneficial effects of NCPAP and contributes to a reduced risk of failure in preterm infants with noninvasive respiratory support. Minimizing the need for invasive mechanical ventilation early in life is an important factor in reducing the risk of BPD and other comorbidities.[21,22]

Systematic reviews with meta-analysis have previously demonstrated the beneficial effects of NIPPV compared with NCPAP in preterm infants. Specifically, NIPPV has been shown to significantly reduce the incidence of extubation failure and the number of apneas.[13,14] The present meta-analysis involved 3 published trials that had evaluated NIPPV compared with NCPAP as an initial respiratory support.[15-17] The first 2 trials found a significant reduction in the need for mechanical ventilation within the first 72 hours of life,[15,16] while the third trial found a significant reduction during the period from 24 to 72 hours.[17] This could be secondary to improved pulmonary mechanics that resulted in better alveolar recruitment. In addition, analysis from the 2 trials[16,17] with the subgroup of infants who received surfactant, suggesting more severe respiratory disease, showed benefits of NIPPV compared with NCPAP, but the difference was not statistically significant.

Bronchopulmonary dysplasia is a complex disorder and remains the most common complication of preterm infants.[2] Studies[3,18] have shown that mechanical ventilation in the first week of life and younger gestational age are the most important predictors of BPD. Normal lung development can be altered by initial lung inflammation and subsequent lung injury. Lung inflammation was shown to be decreased in animal models that were treated initially with noninvasive ventilation compared with mechanical ventilation. Studying surfactant-deficient lambs at 2 hours of life, Jobe et al[23] demonstrated less lung inflammation in CPAP-treated animals. In surfactant-deficient piglets, Lampland et al[24] observed decreased biochemical markers of lung inflammation in animals treated with NIPPV compared with mechanical ventilation. However, more recently, Polglase et al[25] instilled *Escherichia coli* endotoxin (lipopolysaccharide) into the lungs of preterm lambs as a proinflammatory mediator and found comparable effects with NCPAP and with mechanical ventilation. This may suggest a potential protective role of CPAP vs mechanical ventilation in the absence of inflammation.

Noninvasive ventilation has been increasingly used as a strategy to minimize or avoid invasive mechanical ventilation in an attempt to decrease the incidence of BPD. Retrospective studies have documented a decrease in the incidence of BPD with a simultaneous increase in noninvasive ventilation. Dumpa et al[22] demonstrated that infants receiving the most prevalent mode of ventilation support in the first week of life (NIPPV or NCPAP) were less likely to have the outcome of BPD or death compared with those receiving mechanical ventilation. However, 2 RCTs[26,27] that randomized patients to NCPAP or intubation found no difference in the primary outcome of BPD at 36 weeks' postmenstrual age.

Comparing NIPPV with NCPAP in a retrospective study, Bhandari et al[28] demonstrated that in the subgroup of infants having a birthweight of 500 to 750 g, SNIPPV was associated with a significantly lower incidence of BPD. In an RCT, Kugelman et al[15] found a significant decrease in the incidence of BPD among preterm infants randomized to NIPPV compared with NCPAP (2% vs 17%, $P = .03$), and the authors attribute their findings to the reduced rate of endotracheal ventilation in the NIPPV group. In the present meta-analysis considering BPD as supplemental oxygen requirement at 36 weeks' postmenstrual age, 2 of 3 trials included showed a trend to lower rates of BPD in infants randomized to NIPPV. However, no significant difference was found overall, but there was significant heterogeneity ($P = .04$, $I^2 = 69\%$).

The considerable heterogeneity found for this outcome suggests marked variability among the studies.[29] However, these results have to be considered with caution because the 3 trials did not have statistical power for these outcomes and because few infants had a birthweight below 1000 g (rendering them most susceptible to BPD). Another important issue when investigating causes of heterogeneity is the timing and intensity of intervention. After the study period of 72 hours, the infants in the trials could be changed to other modes of respiratory support, suggesting that a longer duration of NIPPV could have been beneficial. More adequately powered studies are needed to assess the outcome of BPD.

There was no significant difference in the incidences of pneumothorax and IVH between the 2 treatment groups. Notably, in a recently reported RCT of NCPAP vs intubation and surfactant, there was a significant increase in pneumothoraces among the NCPAP group.[26] There was no difference in the rates of IVH in the 2 RCTs that randomized patients to NCPAP or intubation.[26,27]

Almost 25 years ago, a study reported an association of gastrointestinal perforations with NIPPV.[30] To our knowledge, this has not been observed in other studies of NIPPV. In a 2011 study[12] comparing infants receiving NCPAP vs NIPPV, no significant differences in abdominal girth were noted between the groups. No infant in the 3 trials included in the present meta-analysis had a gastric or any intestinal perforation. When the time to full feeds was evaluated using data obtained from 2 trials,[15,17] no significant difference was found between the treatment groups, demonstrating the safety of NIPPV. These data suggest that delivering positive-pressure breaths via NIPPV does not prolong the time needed for an infant to reach full feeds. Furthermore, no difference was found between the treatment groups in the incidence of NEC.

Preterm infants encounter a long hospital stay owing to their multiple comorbidities, especially those related to respiratory and feeding complications. Strategies to reduce these complications need to be established early in life. In this meta-analysis, no difference was found between the 2 treatment groups in the duration of hospital stay. However, there was considerable heterogeneity among the trials. This is likely explained by the many variables that are involved in decisions on the length of hospital stay and by the great variation in practices across centers.

The most common form of noninvasive respiratory support used at many centers for preterm infants is NCPAP. However, significant failure rates (range, 30%-60%) of this therapy have been reported, especially in infants younger

than 28 weeks' gestation.[31,32] A potentially useful method to augment the beneficial effects of NCPAP is NIPPV, which may reduce the need for invasive ventilation, especially in infants who initially fail NCPAP. Evidence shows that NIPPV prevents extubation failure, reduces the number of apneas, and, when used as a primary mode of respiratory support, decreases the need for invasive mechanical ventilation. Given the importance of these factors in the pathogenesis of BPD, it is plausible that NIPPV may reduce the incidence of BPD. Larger trials involving the most vulnerable preterm infants with longer periods of intervention are needed to assess the relative merits of these 2 ventilatory strategies.

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