Title

Nasal intermittent positive pressure ventilation as a rescue therapy after nasal continuous positive airway pressure failure in infants with respiratory distress syndrome

Running tittle

Neonatal noninvasive ventilation as a rescue therapy

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Abstract

Objective: Evaluate whether nasal intermittent positive-pressure ventilation (NIPPV) as rescue therapy after initial nasal continuous positive airway (NCPAP) failure reduces need for invasive mechanical ventilation (IMV) in infants with respiratory distress syndrome (RDS). **Design:** Retrospective cohort involving 156 preterm infants who failed initial NCPAP and were then submitted to NIPPV rescue therapy and classified into NIPPV success or failure, according to need for IMV. **Result:** Of all infants included, 85 (54.5%) were successfully rescued with NIPPV while 71 (45.5%) failed. The NIPPV success group had significantly lower rates of bronchopulmonary dysplasia, peri/intraventricular hemorrhage, patent ductus arteriosus and greater survival without morbidities (all $p \leq 0.01$). Infants who failed NIPPV had earlier initial NCPAP failure ($p=0.09$). In final logistic regression model, birthweight ≤1000 g and need for surfactant remained significant factors for NIPPV failure. **Conclusion:** NIPPV rescue therapy reduced the need for IMV in infants that failed NCPAP and was associated with better outcomes.

Key words: noninvasive ventilation, newborn, RDS, NIPPV, NCPAP.

Introduction

Prematurity along with respiratory distress syndrome (RDS) is one of the main causes of neonatal mortality. In recent decades, through the advancement of invasive mechanical ventilation (IMV), surfactant therapy, and the use of antenatal corticosteroids, a reduction in mortality has been achieved [1]. However, with the increased survival of extremely premature infants, some neonatal morbidities are still highly prevalent, especially bronchopulmonary dysplasia (BPD) [2,3]. This condition has a multifactorial origin; however, IMV plays a key role, resulting in inflammation of the lungs and impaired development in the most immature infants [4].

Noninvasive ventilatory support has been extensively studied to minimize the damage caused by IMV and therefore decrease the incidence of BPD [5,6]. The two most studied modes of noninvasive ventilation are nasal continuous positive airway pressure (NCPAP) and nasal intermittent positive-pressure ventilation (NIPPV), which can be administered to the patient through interfaces such as nasal prongs or mask [7].

NCPAP generates a positive end-expiratory pressure (PEEP), to maintain functional residual capacity, preventing alveolar collapse [8]. NIPPV is the application of NCPAP that, in addition to PEEP, provides a superimposed cycled intermittent peak inspiratory pressure (PIP) that may or may not be synchronized with the newborn's inspiratory effort. This pressure increases the mean airway pressure, improving oxygenation and the work of breathing, and recruiting the lung more efficiently than NCPAP alone [8,9].

Despite the available evidence regarding the superiority of NIPPV over NCPAP as both primary [10] and postextubation [11] ventilatory support, NCPAP remains the mainstay of initial noninvasive ventilation for preterm infants. Extensive experience with NCPAP and its safety and cost-effectiveness, have contributed to its wide use in

clinical practice in neonatal units [12]. Studies have shown an early NCPAP failure rate of 50%, leading to the need for tracheal intubation and IMV [13,14]. The use of NIPPV as a rescue therapy in this situation could be an alternative ventilatory strategy that may be capable of avoiding IMV. However, very few studies on the use of NIPPV as a rescue therapy are available [15,16].

The main objective of this cohort study was to evaluate whether the use of NIPPV as a rescue therapy reduces the need for IMV in preterm infants with RDS after initial NCPAP failure.

Materials and methods

This was a retrospective cohort study conducted in a Level III neonatal intensive care unit at the Instituto de Medicina Integral Prof. Fernando Figueira in Recife, Pernambuco, Brazil, from January 2016 to December 2019. A database registry of preterm infants (gestational age or GA <32 weeks) with birthweight (BW) <1500 g was used. Patients were eligible if they received NIPPV during hospitalization and were then selected for an initial analysis of their medical records. Of these, infants with RDS (defined as having respiratory distress within 3 hours of birth with associated radiographic evidence) on NCPAP for initial respiratory support, who failed during the first 120 hours of life and underwent rescue NIPPV were analyzed. Most infants who failed NCPAP were because of the need for 1st dose of surfactant (NCPAP ≥6 cm H_20 and fraction of inspired oxygen or FiO_2 ≥0.3), apnea or increased work of breathing. These patients were followed for a 72-hour period of this rescue NIPPV support and were divided into two groups: NIPPV success or NIPPV failure, based on whether tracheal intubation and IMV were needed at the discretion of the attending neonatologist. The decision to intubate and provide IMV essentially followed

previously published guidelines [17]. Patients with severe congenital malformations were excluded.

In this neonatal unit, the use of noninvasive ventilatory support, including NIPPV as a rescue therapy, is a well-established practice [18]. Nasal CPAP is administered through bubble CPAP or ventilator-derived CPAP, with a flow of 8-10 L/min, PEEP of 5-7 cm H_2O, and FiO_2 necessary to maintain oxygen saturation (SpO_2) between 91% and 95%. A time-cycled, pressure-limited, and continuous-flow neonatal ventilator (Intermed / iX5, Intermed Inc, Sao Paulo, Brazil) with NIPPV in a non-synchronized mode with the following parameters was used: a PIP between 15 and 25 cm H_2O, a PEEP of 5-7 cm H_2O, an inspiratory time (Ti) of 0.4-0.5 s, a flow rate of 8-10 L/min, a frequency of 20-30 breaths/min, and an FiO_2 to maintain SpO_2 between 91% and 95%. Both NCPAP and NIPPV were provided using short bi-nasal prongs (Hudson RCI infant nasal prong cannula) as the nasal interface. Blood gases were done as clinically indicated and utilized to manage NCPAP/NIPPV settings.

The maternal characteristics recorded were the presence of hypertension, diabetes or chorioamnionitis (as defined clinically by the obstetrician), the use of antenatal corticosteroids, and the mode of delivery. GA, BW, BW adequate or small for GA (SGA) [19], Apgar scores at 1 and 5 minutes, Score for Neonatal Acute Physiology with Perinatal Extension (SNAPPE) [20], surfactant use and early-onset clinical neonatal sepsis (defined as the presence of relevant clinical and laboratory findings with or without positive blood culture that required antibiotics for ≥5 days) were recorded as neonatal characteristics. The following neonatal outcomes were evaluated: patent ductus arteriosus (PDA), diagnosed by an echocardiography finding of the presence of a shunt from the descending thoracic aorta to the pulmonary artery; bronchopulmonary dysplasia (BPD), defined as receiving supplemental oxygen at 36 weeks postmenstrual

age (PMA); retinopathy of prematurity (ROP), according to the International Classification of Retinopathy of Prematurity [21]; peri/intraventricular hemorrhage (P/IVH), according to Papile's classification based on cranial ultrasound [22]; necrotizing enterocolitis (NEC), defined as stage 2 and above according to modified Bell staging criteria [23]; late onset sepsis, defined using clinical and laboratorial findings and a positive blood culture; days of oxygen therapy; survival, and survival without major morbidities.

Statistical analysis

Categorical variables were compared using the chi-square association test or Fisher's exact test, and numerical variables using Student's t test and the Mann–Whitney U test. Variables with a significance ≤0.20 in the bivariate analysis were considered in the logistic regression to determine the predictive factors of NIPPV failure and in the final model, they are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A Kaplan–Meier survival curve was used to estimate the time to NCPAP failure in both groups of NIPPV according to the log rank test (Mantel–Cox). All statistical tests were two-sided, with a *P* value of <0.05 deemed significant. Analyses were performed using SPSS for Windows version 21.0 software (IBM Corporation, Armonk, NY).

Results

Of the 523 eligible patients, 156 newborns were included in the study. Of these, 85 (54.5%) did not require tracheal intubation and IMV during the 72-hour period after initiating rescue NIPPV, and therefore constituted the NIPPV success group. The remaining 71 (45.5%) patients failed and were considered NIPPV failure group (**Fig. 1**).

The reasons for NIPPV failure, as described by the attending physician, were the need for a second dose of surfactant (42.3%), apnea (28.2%), increased respiratory effort (22.5%), and nasal septal trauma (7%).

In this study, the mean (± SD) age of the mothers was 26.2 ± 6.9 years, and hypertension was observed in 77 (49.4%) pregnant women. Antenatal corticosteroids were administered to 141 (90.4%) mothers, and 92 (59%) births were by cesarean delivery. The neonates had a mean GA of 28.6 ± 2.0 weeks and a mean BW of 1084.4 ± 227 g; 39 infants (25%) were SGA, and the median SNAPPE II score was 15.5 (8-26). Surfactant administration was done in 104 (66.6%) patients, and the first dose was administered at a median of 5 (1-48) hours of life.

Table 1 shows the variables in the rescue NIPPV success and failure groups. The NIPPV failure group had a significantly younger GA, a lower BW, a greater percentage of newborns weighing ≤1000 g, a higher SNAPPE II score, and a greater need for pulmonary surfactant. A higher percentage of newborns were SGA in the NIPPV success group (p=0.08). No difference in the time to administration of the first surfactant dose was found.

The main neonatal outcomes in both groups of preterm infants are shown in **Table 2**. Patients in the NIPPV failure group had higher rates of BPD, P/IVH, and PDA (all $p \leq 0.01$). Survival and survival without major morbidities were significantly (both $p \leq 0.01$) higher in the successful NIPPV group.

In the final logistic regression model, the following variables remained significant for NIPPV failure: birth weight ≤1000 g and the need for surfactant (**Table 3**).

The Kaplan–Meier survival curve demonstrates that NCPAP failure occurred earlier in premature infants who subsequently failed rescue NIPPV than in those who had success, although the difference was not statistically significant (p=0.09) (**Fig. 2**).

Discussion

In this study, NIPPV as a rescue therapy reduced the need for tracheal intubation and IMV in 85 (54.5%) of 156 neonates who failed NCPAP as a primary mode of respiratory support. Additionally, this group had better neonatal outcomes than the 71 (45.5%) neonates in the group that failed NIPPV rescue therapy.

Studies have shown promising results for NIPPV as a noninvasive respiratory support in some clinical settings [24-26]. Therefore, it is plausible to acknowledge its beneficial effects and indications in other situations, such as NIPPV rescue therapy. Preterm infants on NCPAP as a primary respiratory mode presenting apnea, requiring an increasing FiO_2 or showing increased work of breathing are considered to have failed NCPAP and are commonly subjected to endotracheal intubation [27,28]. NIPPV may be used as a rescue therapy, augmenting the effectiveness of noninvasive respiratory support and therefore avoiding mechanical ventilation [29].

Ramos-Navarro et al. [15] evaluated the use of NIPPV as rescue therapy after initial NCPAP failure in a prospective observational study, and invasive ventilation was avoided in 16 (69.5%) of the 23 patients. Badiee et al. [16] analyzed data from 27 patients and found a 74% success rate with rescue NIPPV after initial NCPAP failure. Both studies reported a higher rate of NIPPV success compared to the present study (54.5%). However, the studies included a small number of patients, and one of them used NIPPV in synchronized mode [15].

In this retrospective cohort, the cesarean section rate was 59%, which can be explained by the presence of maternal comorbidities, particularly the high rate of hypertension (49.4%), which may have contributed to the significant percentage of SGA newborns (25%). The effects of intrauterine fetal restriction on lung development have not been fully elucidated [30] and some authors have found it to be a protective factor for RDS [31]. We found a higher rate of SGA newborns (p=0.08), as well as a higher GA (p<0.01) in the NIPPV success group.

Patients with advanced resuscitation who are intubated in the delivery room, were not included in the study, which is consistent with the median Apgar scores of 7 and 9 in the first and fifth minutes, respectively, in both groups. The SNAPPE II severity score was significantly higher in the NIPPV failure group; on the other hand, no difference was found regarding early-onset sepsis, which is also a risk factor for a more initially severe clinical condition [32,33].

In this cohort, infants in the NIPPV failure group had a significantly lower GA and BW than those in the NIPPV success group, which was also demonstrated in a subgroup of patients with a BW ≤1000 g. Badiee et al. [16] found a similar result, although it was not statistically significant. Preterm birth at such a critical time of lung development, along with very low BW, are important factors that may contribute to the inadequate response to rescue NIPPV. Some authors support that synchronized NIPPV (SNIPPV) may further improve NIPPV efficacy with more efficient positive pressure transmission to the lung and better stabilization of the chest wall during inspiration, reducing intubation rates [34,35]. Others have not found SNIPPV vs NIPPV to be associated with a differential impact on clinical outcomes [36]. In this study, non-synchronized NIPPV was used because of the lack of availability of the appropriate

ventilator, which is the most commonly used mode of NIPPV in neonatal practice [34,36].

In recent years, the use of antenatal corticosteroids combined with noninvasive ventilation and pulmonary surfactant has improved neonatal outcomes [25,37,38]. Among the 156 newborns in this study, 141 (90.4%) were exposed to antenatal corticosteroids, and 104 (66.6%) required exogenous surfactant replacement. In the present study, greater use of pulmonary surfactant (84.5% vs 50.6%, $p<0.001$) and later treatment in hours of life (5 vs 6, $p=0.54$) were found in the NIPPV failure group, than in the success group. The greater use of surfactant as well as early administration suggests increased severity of lung disease and might be considered risk factors for NIPPV failure in these patients.

It is known that IMV is associated with several neonatal morbidities, including BPD, P/IVH, ROP, and NEC [39,40]. In a Cochrane review by Lemyre et al., despite showing that NIPPV reduced tracheal intubation rates compared to NCPAP, as primary modes of respiratory support, they did not find a decrease in the incidence of BPD [10]. However, a recent meta-analysis demonstrated a lower incidence of the composite outcome, BPD or death, with the use of NIPPV compared to NCPAP (0.74 [0.52, 0.98]) [41].

In this study, the NIPPV success group had better outcomes regarding BPD, P/IVH, PDA, survival, and survival without major morbidities suggesting that this ventilatory support strategy may be an option for patients with initial NCPAP failure. Even though the duration of oxygen therapy was significantly higher in the NIPPV failure group, we did not find a difference in the incidence of ROP ≥ stage 3. In most neonatal units it is current practice that initial NCPAP failure in preterm infants with RDS is an indication for tracheal intubation and IMV. The use of NIPPV as rescue

therapy might offer preterm infants with RDS an alternative ventilatory strategy to prevent invasive ventilation and adverse neonatal outcomes.

Despite the wide use of noninvasive ventilation, a percentage of newborns will eventually fail this respiratory support, including NIPPV [39,41]. In our cohort, preterm infants with BW ≤1000 g and those who required pulmonary surfactant had a significantly higher likelihood of rescue NIPPV failure. We also observed that patients who failed rescue NIPPV also had earlier failure of initial NCPAP (p=0.09). Navarro et al. [15] found similar results when comparing NIPPV success rates between preterm infants who failed initial NCPAP before or after 3 days, demonstrating higher NIPPV success when NCPAP failure occurred after 3 days. A low BW, the need for pulmonary surfactant and early NCPAP failure suggest greater severity of lung disease. Studies are needed to identify which group of premature infants would most benefit from rescue NIPPV, and thus reduce the risks of IMV.

Our study has some limitations. Its retrospective design precludes us from identifying the exact criteria used for NCPAP failure. While our unit has a protocol for indicating NIPPV rescue after NCPAP failure, the decision to do so was dependent on the judgement of the attending physician. It is also limited by the unavailability of additional information such as specific ventilatory or blood gas parameters.

Very few studies regarding rescue NIPPV after initial NCPAP failure are available. This study describes the largest cohort to date of infants with NIPPV used as a rescue therapy, which was performed in a neonatal unit with extensive clinical experience with NIPPV, either as a primary mode, post-extubation, or after NCPAP failure.

The use of rescue NIPPV decreased the need for invasive ventilation and associated morbidities in preterm neonates who failed initial NCPAP. Studies should be

conducted to identify infants who would most benefit from this noninvasive ventilatory strategy in a safe and effective manner.

Additional information

Conflict of interest

The authors declare no competing financial interests

Ethics approval and consent to participate

The research complied with the ethical principles established in the Declaration of Helsinki and was submitted to the ethics committee of the Instituto de Medicina Integral Professor Fernando Figueira, IMIP, Recife, Brazil. CAAE: 27431919.0.0000.5201.

Availability of data and materials

The authors acknowledge that the data and materials are available to referees at submission and to readers promptly upon request.

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Author contributions

CI conceptualized the study, participated in the study design, data collection and data analysis, and wrote and revised the paper. JM conceptualized the study, participated in the study design and data analysis, and wrote and revised the paper. JA participated in the study design, data analysis and revision. JC participated in the study design and data collection. EA participated in the data analysis. VB conceptualized the study, participated in the study design, and revised the paper.

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