Nasal intermittent positive pressure ventilation during less invasive surfactant administration in preterm infants: An open-label randomized controlled study

NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION DURING LESS INVASIVE SURFACTANT ADMINISTRATION IN PRETERM INFANTS: AN OPEN-LABEL RANDOMIZED CONTROLLED STUDY

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ABSTRACT

Introduction: Approximately half of very preterm infants with respiratory distress syndrome (RDS) fail treatment with nasal continuous airway pressure (NCPAP) and need mechanical ventilation.

Objectives: Our aim with this study was to evaluate if nasal intermittent positive pressure ventilation (NIPPV) during less invasive surfactant treatment (LISA) can improve respiratory outcome compared with NCPAP.

Materials and Methods: We carried out an open-label randomized controlled trial at tertiary neonatal intensive care units in which infants with RDS born at 25^{+0}-31^{+6} weeks of gestation between 1 December, 2020, and 31 October, 2022 were supported with NCPAP before and after surfactant administration and received NIPPV or NCPAP during LISA. The primary endpoint was the need for a second dose of surfactant or MV in the first 72 h of life. Other endpoints were need and duration of invasive and noninvasive respiratory supports, changes in SpO_2/FiO_2 ratio after LISA, and adverse effect rate.

Results: We enrolled 101 infants in the NIPPV group and 99 in the NCPAP group. The unadjusted odds ratio for the composite primary outcome was 0.873 (95% CI 0.456-1.671; P=0.681). We found that the SpO_2/FiO_2 ratio was transiently higher in the LISA plus NIPPV than in the LISA plus NCPAP group, while adverse effects of LISA had similar occurrence in the two arms.

Conclusions: The application of NIPPV or NCPAP during LISA in very preterm infants supported with NCPAP before and after surfactant administration had similar effects on the short-term respiratory outcome and are both safe. Our study does not support the use of NIPPV during LISA.

Trial registration NCT05796128.

1. INTRODUCTION

Preterm birth before 32 weeks of gestational age is often complicated by respiratory distress syndrome (RDS) due to surfactant deficiency and immaturity of the respiratory system [1]. Currently, RDS can often be treated with noninvasive respiratory supports, such as nasal continuous positive airway pressure (NCPAP) starting in the delivery room immediately after birth [2]. The treatment with surfactant in association with noninvasive respiratory supports is effective in reducing the need for mechanical ventilation (MV) by favoring the improvement of functional residual capacity (FRC) and pulmonary compliance [3]. Recently, the so-called "less invasive surfactant administration strategy" (LISA), which involves the use of thin catheters that are placed in the trachea for a very short time, has become widespread [4]. The technique involves continuing NCPAP during the administration of the surfactant and could have the advantage over the INtubation-SURfactant-Extubation (InSURE) procedure of limiting the possible complications related to tracheal intubation and MV prolongation after surfactant administration [4]. Although this issue is still under debate [4,5], a recent meta-analysis reported that the LISA strategy decreases the risk of MV, death, and bronchopulmonary dysplasia (BPD) in survivors [6].

Very preterm infants can have ineffective spontaneous respiratory activity such that, despite NCPAP contributing to the prevention of the alveolar collapse in the expiratory phase, they are often unable to generate adequate tidal volume (TV) and minute ventilation to ensure normal gaseous exchanges [7]. Therefore, approximately 50% of very low birth weight infants treated with NCPAP fail and must be intubated to initiate MV [8]. Nasal intermittent positive pressure ventilation (NIPPV) is a time cycled, pressure limited mode of ventilation which provides a backup rate with adequate peak inspiratory pressure (PIP) able to generate a TV [9]. It has been reported that NIPPV offers all of the benefits of NCPAP with a further decrease in upper airway resistance and an increase of spontaneous inspiratory effort, FRC, TV, and minute volume [9]. Consistently, NIPPV has been found to be more effective than NCPAP in preventing MV [10] and extubation failure [11], and previous studies demonstrated that surfactant treatment with LISA technique during NIPPV was effective in both an animal model [12] and very preterm infants [13].

Thus, we hypothesized that the benefits of NIPPV over NCPAP might also affect the time period of surfactant administration during LISA procedure and that the delivery of a proper TV can allow a better surfactant lung deposition and distribution. To evaluate this hypothesis, we planned a randomized controlled trial in which we compared the effect of using NIPPV versus NCPAP during LISA on respiratory outcome in very premature infants with RDS (NIPAL study: Nasal Intermittent positive pressure ventilation versus nasal continuous Positive Airway pressure during Less invasive surfactant administration).

2. MATERIALS AND METHODS

2.1 Study Design

We performed a national, multicenter, randomized trial in neonatal intensive care units (NICUs) after the approval of local ethics committees. Infants with gestational age 25^{+0}-31^{+6} weeks were enrolled in the study within the first 6 h of life, if they were affected by RDS requiring NCPAP and FiO_2 >0.30 and had been treated with intravenous caffeine (Peyona®, Chiesi, Parma, Italy; loading dose 20 mg/kg, maintenance dose 5 mg/kg). RDS was defined as the presence of clinical signs of respiratory distress, oxygen-dependence during the first 24 h of life, consistent chest radiograph appearances (decreased lung air content, reticulogranular pattern of the lungs, and air bronchograms), and the exclusion of other causes of respiratory failure [14]. Exclusion criteria were need for MV, major congenital malformations, chromosomal disorders, previous surfactant treatment, cardiovascular instability requiring vasoactive drugs, air leaks, and death within the first 72 h of life.

Information, in written and oral form, was offered to all parents prior to birth during antenatal controls if there was a risk of preterm delivery or at mother's hospital admission in case of sudden delivery. Sufficient time was allowed for consent and both parents signed an informed written consent form.

2.2 Randomization

Infants were randomized to receive NIPPV or NCPAP during LISA in a 1:1 ratio in permuted blocks of variable size using an electronically generated sequence. Randomization was stratified according to center and gestational age (25^{+0}-28^{+6} and 29^{+0}-31^{+6} weeks).

2.3 Study Intervention

Enrolled infants underwent surfactant treatment (Curosurf®, Chiesi, Parma, Italy: 200 mg/Kg) with LISA technique and received 5-8 cm of H_2O NCPAP or NIPPV [synchronized (sNIPPV) or not] set at a respiratory rate (RR) of 40 breaths/min, positive end-expiratory pressure (PEEP) of 5 cmH_2O, positive inspiratory pressure (PIP) of 20 cmH_2O, and inspiratory time of 0.35 sec throughout the procedure. The surfactant was instilled slowly (0.5-3 min) using a thin catheter (LISAcath®, Chiesi, Parma, Italy) which was inserted after analgosedation (performed according to local protocols) into the patient's trachea via direct laryngoscopy. Then, all infants resumed NCPAP at the pre-LISA

pressure level. Subsequent changes of noninvasive respiratory supports [NIPPV, sNIPPV, bi-level CPAP (BiPAP)] were performed based on local protocols.

A second dose of surfactant (100 mg/Kg) was allowed in patients with FiO_2 >0.30 not requiring MV and was given using the same methods of the first dose. Additional doses were given at attending neonatologist's discretion.

Infants were started on MV [patient triggered ventilation (PTV) with or without volume guarantee (VG) or high frequency ventilation (HFV)] when pH was <7.20 with $PaCO_2$ >65 mmHg, or PaO_2 <50 mmHg with $FiO_2 \geq 0.50$ after surfactant treatment, or if infants had frequent episodes of apnea (>4 episodes in 1 h, or >2 episodes requiring bag-and-mask ventilation). Respiratory supports were set to maintain a $PaCO_2$ of 55-65 mm Hg and 90-95% SpO_2.

2.4 Outcomes

The primary endpoint of our study was the need for a second dose of surfactant or MV within the first 72 h of life. Prespecified secondary endpoints were the components of the composite primary endpoint, need and duration of invasive and noninvasive respiratory supports, changes in SpO_2/FiO_2 ratio after LISA, occurrence of BPD, and adverse effect rate.

2.5 Other Collected Data

We recorded the following data for each infant: gestational age, birth weight, birth weight <10th percentile for gestational age, sex, singleton or twin, occurrence and duration of noninvasive and invasive (MV) respiratory support, age at start of MV, number of doses of surfactant and age at the 1st administration, LISA procedure duration, occurrence of PDA requiring pharmacological treatment, grade 3-4 intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), BPD, sepsis, length of stay in hospital, and mortality. The adapted classification of Papile et al. was used to classify IVH [15], and periventricular leukomalacia was diagnosed in agreement with De Vries et al. [16]. The diagnosis of necrotising enterocolitis was made according to Bell's criteria [17]. The retinopathy of prematurity was evaluated in accordance with the International Classification of ROP [18]. BPD was defined and graded as mild, moderate, or severe based on the classification of Jobe et al [19]. The diagnosis of sepsis was based

on clinical and laboratory data (total neutrophil count, C-reactive protein, procalcitonin) confirmed by the presence of at least one positive blood.

The examined maternal variables included antenatal steroid treatment, type of delivery, placental abruption, hypertensive disorders, prolonged premature rupture of membranes (pPROM) >18 h, clinical chorioamnionitis (defined as the presence of fever with one or more of the following: maternal leukocytosis >15,000/ mm^3, uterine tenderness, fetal tachycardia, or foul-smelling amniotic fluid), and gestational diabetes.

We also recorded the highest FiO_2 and lowest SpO_2/FiO_2 ratio to evaluate RDS severity, and SpO_2/FiO_2 ratio before and 6 (T_{6h}), 12 (T_{12h}), 18 (T_{18h}), 24 (T_{24h}), 30 (T_{30h}), 36 (T_{36h}), 42 (T_{42h}) h after LISA procedure to evaluate changes of oxygenation in the study groups.

Adverse effects potentially associated to LISA procedure, such as bradycardia (HR <80 bpm), hypoxia (SpO_2 <80% for >20 sec), laryngospasm, vomit, surfactant overflow and pneumothorax (within 24 h from LISA procedure) were also reported.

2.6 Statistical Analysis

On the basis of data from a previous study [20], we hypothesized that NIPPV might decrease the need for a second dose of surfactant or MV during the first 72 h of life from 50% to 30%. In fact, we considered this decrease to be the minimal clinically important difference between the two study arms. We calculated the need to enrol 93 newborns in each group to detect this difference as statistically significant at two-sided 0.05 level with 80% power. Therefore, considering a dropout of 10%, it was planned to enroll 102 patients per group. However, the trial was stopped early after enrolment of 202, instead of 204 participants, because the LISACath® was withdrawn from the market.

Data analysis was performed according to the intention-to-treat (ITT) principle, whereas we planned in advance to perform per-protocol (PP) data analysis only if the ITT and PP sample size populations differed by >5%. Categorical baseline characteristics were summarized as frequencies and percentage. Continuous variables were reported as mean and standard deviation. Proportions were compared using the standard chi-square test for heterogeneity or, when appropriate, the Fisher's exact test. The Wilcoxon rank-sum test was used to compare continuous outcomes. Unadjusted

odds ratios with 95% confidence limits were estimated according to a logistic regression model for treatment comparisons of the main dichotomous outcomes between the two study groups. The Wald chi-square test was used to quantify the statistical significance of all coefficients. The estimates of the odds ratios adjusted for clinical site and gestational age (25^{+0}-28^{+6} and 29^{+0}-31^{+6} weeks) were calculated according to a logistic regression model with clinical site treated as a random effect. Subgroup analyses were performed by means of an interaction test to determine the consistency of the treatment effect according to the gestational age. All statistical tests were two-sided, and P values $\leq$0.05 were considered to be statistically significant. No adjustment for multiple comparisons was made. Statistical analyses were performed by LB using SAS version 9.4 (SAS Institute, Cary, NC).

3. RESULTS

The numbers of infants deemed eligible for the study and the numbers randomly assigned to receive NCPAP or NIPPV during LISA are shown in the Consort flow diagram (Fig. 1). A total of 202 infants was enrolled between 1 December, 2020, and 31 October, 2022. Two infants erroneously randomized twice were excluded from the ITT population. ITT and PP populations differed by 0.5% (1/200) and, therefore, PP data analysis was not performed. All patients were followed up to their discharge, and no violations of criteria for giving the second dose of surfactant and starting MV were reported. The baseline characteristics of infants at birth and of their mothers were similar in the two groups (Table 1).

The rate of composite primary outcome was similar in the NCPAP and NIPPV group (25 vs. 23%) with an unadjusted odds ratio between the groups of 0.873 (95% CI 0.456-1.671; P=0.681). Similarly, the unadjusted odds ratio for the need of a second dose of surfactant (1.339, 95% CI 0.612-2.927; P=0.464) and MV (0.847, 95% CI 0.405-1.774; P=0.660) within the first 72 h of life did not differ between the two groups. Age at LISA and age at start of MV and its duration were similar in the NCPAP and NIPPV groups (Table 2). The comparison was not substantially changed by adjustment with the use of logistic regression, as described.

The effect of gestational age on the primary endpoint was similar in both groups (P=0.381), as well as the effect on the need for a second dose of surfactant (P=0.479). However, there was a trend toward a decrease of the need for MV within the first 72 h of life in infants born at 29-31 weeks of gestation (unadjusted OR 0.555, 95% CI 0.188-1.164) that we did not observe among infants born at 25-28 weeks of gestation (unadjusted OR 1.250, 95% CI 0.437-3.575), although the heterogeneity of the treatment effect did not result statistically significant (P=0.292; interaction test) (Table 3).

Need and duration of invasive and noninvasive respiratory supports as well as the need and number of doses of surfactant did not differ in the two treatment groups (Table 2). In detail, a single dose of surfactant was given to 86 (n=85) and 82% (n=83) of patients in the NCPAP and NIPPV groups, while 10 (n=10) and 14% (n=14) needed two doses, and 4 (n=4) and 4% (n=4) needed three or more doses, respectively.

We found that 27% (n=27) of surviving infants in the NCPAP group had BPD in comparison with 31% (n=31) in the NIPPV group (P=0.362) without differences of severity. There were no differences of prematurity complication rate, and six infants in the NCPAP group and eight in the NIPPV group died during the study (cumulative mortality during in hospital stay 8% vs. 11%, P=0.606) (Table 4). The SpO_2/FiO_2 ratio was transiently higher at T_{6h} (398±78 vs. 381±77, P= 0.043) and T_{30h} (414±63 vs. 397±67, P=0.019) in the NIPPV than in the NCPAP groups (Table 5; Fig. S1), while adverse effects of LISA had similar occurrence in both the groups (Table S1).

4. DISCUSSION

In this study, we compared the effect of LISA plus NIPPV versus LISA plus NCPAP on respiratory outcome in a population of very premature infants with RDS who were supported with NCPAP before and after surfactant administration. We found that the two strategies had similar effects on both the composite outcome of need for a second dose of surfactant or MV within the first 72 h of life and its individual components.

Our hypothesis, that NIPPV in the course of LISA procedure might decrease the need for surfactant and MV, was based on the fact that this noninvasive respiratory support allows a decrease of respiratory airway resistance and development of a TV while a continuous positive end expiratory pressure (PEEP) is delivered [9], and that this might favor a higher and more homogeneous lung surfactant deposition. In fact, it has been reported that preterm lambs who received LISA procedure with NCPAP have a lower surfactant lung deposition than animals who received surfactant after intubation and MV [7]. On the other hand, Ricci et al. demonstrated in adult rabbits with RDS that surfactant deposition is similar using the LISA or the InSURE procedure [21], but underlined that the difference of surfactant deposition observed in their work compared with Niemarkt's study [7] might be explained by the duration of LISA procedure in their protocol (2 vs. 1 min) and the use of a video laryngoscope to optimize surfactant delivery [21]. Thus, it could be inferred that changes in the procedure (i.e.: NIPPV instead of NCPAP) could improve the LISA success rate. Unfortunately, results of our study disproved our hypothesis and, to explain them, we can offer some speculations: NIPPV during LISA may have enhanced surfactant deposition not enough to achieve clinical effects in infants with more severe surfactant deficiency; this hypothesis can be supported by the observed trend toward a decrease in the need for MV in less immature infants (29-31 weeks of gestation) who are expected to have a lower surfactant deficiency and by the transient improvement of oxygenation in the NIPPV group. Another possible explanation is the very limited use of synchronized NIPPV (S-NIPPV) in our patients, as only one of participating centers used S-NIPPV during LISA. In fact, favorable effects of S-NIPPV are commonly related to the fact that synchronization with spontaneous breathing allows transmission of positive pressure to the distal airways and alveoli, through a patent glottis and low-resistant upper airways, and the achievement of an adequate TV more effectively

than NIPPV [22]. Thus, it is possible that S-NIPPV may improve surfactant deposition with LISA limiting asynchrony between spontaneous and supported breathing [22]. However, while advantages of S-NIPPV in the treatment of infants with RDS are confirmed by meta-analyses [10,11], its possible benefit during LISA remained to be demonstrated.

Our findings cannot be compared to previous studies since this study is the first in which preterm infants supported with NCPAP before and after surfactant administration received NIPPV only during LISA. In fact, Oncel et al. treated very preterm infants with NCPAP or NIPPV as initial noninvasive support, during LISA, and eventually after MV, and not only during LISA [12]. Similarly, Ricci et al. demonstrated in animals with RDS treated with surfactant that S-NIPPV improves lung mechanics and gas exchanges compared to NCPAP and NIPPV, but noninvasive ventilation was started following MV and after surfactant was given just prior to extubation [23].

In our study, the occurrence of adverse effects of LISA was strictly monitored to ascertain whether the application of NIPPV during LISA was safe. We found that the adverse effect rate was similar in the NIPPV and LISA groups and their frequency was similar to that previously reported [24]. These results are interesting considering that all our patients received analgosedation during LISA which does not seem to induce a significant increase of adverse effects.

4.1 Generalizability of the study

This study can be replicated in tertiary-level NICUs provided NIPPV facility should be available.

4.2 Strength of the study

This is the first study which compared the effect of LISA plus NIPPV versus LISA plus NCPAP in very preterm infants supported with NCPAP before and after surfactant administration.

5. LIMITATION

The proportion of primary outcome failures observed in the control arm is substantially lower than that expected when the study was designed. This only apparently affects the statistical power of the study. In fact, with the size of the enrolled population the present study maintains a statistical power adequate to detect an absolute reduction of failures equal to or greater than 16%.

Limitations of the study also include a lack of intervention blinding. However, the decision to start MV and give a second dose of surfactant was made by clinicians other than the investigators involved in the study, and researchers assessing study endpoints and the data manager were blinded to the nature of the study treatments.

6. CONCLUSIONS

We found that the application of NIPPV or NCPAP during LISA in very preterm infants supported with NCPAP before and after surfactant administration had similar effects on the short-term respiratory outcome. Therefore, our study does not support the use of NIPPV during LISA. Our data contributes to improving knowledge on an important aspect of LISA procedure, such as the most effective noninvasive respiratory support during its execution.

CONFLICT OF INTERESTS

Prof. Carlo Dani received honoraria from Chiesi Farmaceutici SpA and Vyaire Medical Inc. for scientific consultancies. Other authors declare that there are no conflicts of interests.

AUTHOR CONTRIBUTIONS

Conceptualization/design: CD, MN, GS, FM, EG, LC, GV, LB, GL; Methodology: CD, LB; GL; Investigation: MN, CB, AM, GN, GS, EB, SG, FC, CF, EP, RB, MC, MF, AL, LB, PB, CM, SV, GM, RF, PL; Supervision/oversight: CD, FM; GL; Funding acquisition: CD, GL; Data curation: CD, LB; Formal analysis: LB; Writing – drafting the initial manuscript: CD; Writing – review or editing of manuscript: CD, MN, CB, AM, GN, GS, EB, SG, FC, CF, EP, RB, MC, MF, FM, AL, EG, LB, PB, CM, LC, SV, GV, GM, RF, PL; GL; Give final approval of the version to be published: All authors; Agree to be accountable for all aspect of the work: All authors.

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Figure 1. CONSORT diagram. NCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation.