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Nasal Intermittent Positive Pressure Ventilation (NIPPV) Vs. Nasal Continuous Positive Airway Pressure (NCPAP) after Less Invasive Surfactant Administration (LISA) in Preterm Infants with Respiratory Distress Syndrome

Mohammad Kazem Sabzehei[1], Behnaz Basiri[1], Mojdeh Afkhami Goli[1], *Maryam Shokouhi Solgi[1], Fatemeh Eghbalian[1], Abbas Moradi[2]

[1] Department of Pediatrics, Hamadan University of Medical Sciences, Hamadan, Iran.

[2] Department of Community Medicine, Hamadan University of Medical Science, Hamadan, Iran.

Abstract

Background: There is insufficient evidence supporting the superiority of the Nasal Intermittent Positive-Pressure Ventilation (NIPPV) over the Nasal Continuous Positive Airway Pressure (NCPAP) in initial respiratory support of preterm neonates suffering from the Respiratory Distress Syndrome (RDS). The present study intended to compare the effectiveness of these two approaches in preterm neonates with RDS who receive the Less Invasive Surfactant Administration (LISA).

Methods: The present clinical trial included 95 preterm neonates at the Fatemieh Hospital, Hamadan, Iran, from October 2019 to September 2020, with RDS, admitted to the Neonatal Intensive Care Unit. Sampling was performed using the convenience method. The participants were randomly assigned into two groups that received the NIPPV (n=48) or NCPAP (n=47) as the respiratory support method. Moreover, the neonates received LISA if needed. The groups were compared in the outcomes, such as the need for intubation within 72 hours after birth.

Results: The groups were similar in clinical characteristics at birth. According to our findings, the NIPPV group had a significantly lower rate of need for intubation and invasive mechanical ventilation within 72 hours after birth compared to the control group (8.3% vs. 27.7%, P=0.014); however, the groups were not significantly different regarding the need for the second dose of surfactant (66% vs. 56.2%, P=0.332), the mean respiratory support duration (6.89±3.20 vs. 6.70±3.71 days, P=0.295), the mean hospital stay (19.52±12.364 vs. 17.40±9.57 days, P=0.591), development of bronchopulmonary dysplasia (4.2% vs. 8.5%, P=0.435), and mortality (6.25% vs. 12.8%, P=0.317).

Conclusion: Compared to NCPAP, the NIPPV could significantly reduce the need for invasive mechanical ventilation within 72 hours after birth in neonates undergoing LISA.

Key Words: LISA, NCPAP, NIPPV, Preterm infants, RDS.

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Corresponding Author:

Maryam Shokouhi Solgi, Department of Pediatrics, Hamadan University of Medical Sciences, Hamadan, Iran. Email: shokohisolgi@umsha.ac.ir

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1- INTRODUCTION

Non-invasive respiratory support methods, such as the Nasal Continuous Positive Airway Pressure (NCPAP), are the most important strategies in managing the Respiratory Distress Syndrome (RDS) in affected preterm neonates (1, 2). As an alternative for the routine technique of endotracheal intubation for surfactant administration in preterm neonates with RDS, the use of NCPAP immediately after birth is recommended by the American Academy of Pediatrics (AAP) (3). Compared to intubation and subsequent mechanical ventilation, early use of NCPAP can further decrease the risk of death and BPD (4, 5). However, the NCPAP still has a relatively high failure rate, especially in extremely preterm neonates (6).

Some recent studies have reported higher benefits of Nasal Intermittent Positive-Pressure Ventilation (NIPPV) compared to NCPAP in reducing the need for endotracheal intubation within the first 72 hours after birth (7, 8). However, Meneses et al. (9) reported that compared to NCPAP, the NIPPV could not reduce the need for invasive ventilation or BPD in the first 72 hours after birth.

Recently, Minimally Invasive Surfactant Therapy (MIST) or Less Invasive Surfactant Administration (LISA) methods, which use a thin catheter under direct laryngoscopy without forceps for surfactant administration, have replaced the INtubation-SURfactant-Extubation (INSURE) technique for RDS treatment. Some clinical trials have shown the effectiveness of these methods in reducing the need for mechanical ventilation and BPD (10, 11). Ramanathan et al. (12) showed the higher effectiveness of NIPPV and NCPAP compared to INSURE and recommended performing further studies comparing the NIPPV and NCPAP in neonates treated with LISA. Given that LISA has been less frequently performed in the healthcare facilities of Iran, the present study intends to investigate some therapeutic outcomes in the neonates treated with LISA who are receiving one of the two respiratory support methods of NCPAP and NIPPV.

2- MATERIALS AND METHODS

2-1. Study design and population

The present clinical trial included 95 premature neonates with 28 to 36 weeks of age suffering from RDS who were admitted to the NICU of the Fatemieh Hospital of the Hamadan University of Medical Sciences from October 2019 to September 2020.

2-2. Sampling

Each neonate was randomly assigned to one of the NCPAP or NIPPV groups with a 1:1 ratio using the sequence number randomization method performed by a computer. The blinding was performed using a sealed envelope with a serial number. The data collector and statistical analyst were not aware of the participant allocation. A study by Shah et al. (13) reported that 17% and 42% of the participants undergoing NIPPV and NCPAP, respectively, needed mechanical ventilation through endotracheal intubation. Given the results of the mentioned study, the sample size equation in comparison of the ratio in both groups, and the types 1 and 2 errors of 0.05 and 20%, respectively, the sample size was estimated at 48 for each group.

α= 5 %, β= 20 %, P1=17%, P2=42%

$$n=\frac{\left(z_{1-\frac{\alpha}{2}}+z_{1-\beta}\right)2(p_1(1-p_1)+p_2(1-p_2))}{(p_1-p_2)2}$$

n=48

$$\frac{(1.96+0.84)2(0.17(0.83)+0.42(0.58))}{(0.42-0.17)2}$$

2-2-1. Inclusion and exclusion criteria

Inclusion criteria: Premature neonates with a gestational age of 28-36 weeks who showed the signs of respiratory distress with Downes score ≥ 3 at birth but did not need intubation in the delivery room were eligible to participate in the study.

Exclusion criteria: The neonates who needed intubation in the delivery room, congenital heart disease, multiple anomalies, a 5-minute Apgar score of ≤4, or were born out of the Fatemieh Hospital were excluded.

2-3. Procedure

The neonates were stabilized in the delivery room or while transferred to the NICU with NCPAP (Neopuff; Fisher & Paykel Healthcare, Auckland, New Zealand). Then, they were randomly assigned to one of the NCPAP or NIPPV groups for respiratory support. In the NCPAP group, which was considered as the control group, the continuous positive airway pressure was applied through the nasal prongs using an NCPAP device (Sindi® Driver, Medin CPAP devices, Germany) with the following settings: positive end-expiratory pressure(PEEP): 5-6 cm H_2O, flow: 5-6 lit/min, Fraction of Inspired Oxygen (FiO_2): 0.21-0.50. In the NIPPV group, which was considered as the intervention group, the neonates were ventilated using a neonatal ventilator (Fabian, ACUTRONIC Medical Systems, and Switzerland) that applied an intermittent positive-pressure ventilation through the nasal prongs. The settings of the device were as follows: Peak Inspiratory Pressure (PIP): 18-20 cm H_2O, PEEP: 5-6 cm H_2O, Respiratory Rate (RR): 30-40 bpm, inspiratory time (Ti): 0.35-0.40 s, flow: 6-5 lit/min. The FiO_2 was titrated at 0.21-0.50 to maintain an oxygen saturation of 90%-95%. To prevent the accumulation of gas in the neonates' stomachs, an orogastric tube was placed.

If the respiratory distress of the neonates in the control group was improved and they had no apnea, bradycardia, or increased Work of Breathing (WOB), the FiO_2 was gradually decreased to 30%. Then, the PEEP was decreased by 1-2 cm H_2O per day to reach a pressure of 4 cm H_2O. If a neonate could maintain an oxygen saturation of 90%-95% with a PEEP of 4 cm H_2O and a FiO_2 of 21%, the neonate was weaned from the CPAP.

If the respiratory distress of the neonates in the intervention group was improved and they had no apnea, bradycardia, or increased work of breathing, the PIP was decreased 2 cm H_2O to reach 14. Then, the respiratory rate was decreased by 5-10 units each time. If the neonate was hemodynamically stable with a PIP of ≤14 cm H_2O, a PEEP of 4 cm H_2O, a RR of ≤20 bpm, and a FiO_2 of 21%, the neonate was weaned from the ventilator.

The neonates under the non-invasive ventilation received surfactant as the rescue treatment if a FiO_2 ≥0.40 was needed to maintain an oxygen saturation level of 90%-95%. 6 hours after the first dose of surfactant, the neonates received a second dose if they needed a FiO_2 ≥0.30 to maintain the target level of oxygen saturation. To perform LISA, a 5F feeding tube was gently passed through the vocal cords by direct laryngoscopy and 200 mg / kg exogenous surfactant (Curosurf; Chiesi Farmaceutici, Parma, Italy) was administered. The neonates received 20 mg/kg of caffeine as a loading dose and then 5 mg/kg daily until the gestational age of 34 weeks.

The failure of non-invasive respiratory support in the neonates undergoing NCPAP or NIPPV was defined with a poor respiratory drive, a need for endotracheal intubation, and subsequent invasive mechanical ventilation. The decision for

intubation was made based on the following standard criteria: severe respiratory acidosis (pH<7.2, pCO_2>60 mm Hg), an arterial oxygen saturation <90% on FiO_2 >50% by pulse oximetry, severe apnea and bradycardia, severe respiratory distress, pulmonary hemorrhage, or cardiopulmonary arrest not responding to resuscitation.

The primary outcome was considered as the need for intubation within 72 hours after birth (failure of non-invasive respiratory support), while the secondary outcomes included the mean duration of non-invasive respiratory support, the mean hospital stay, development of pneumothorax, BPD, Intraventricular Hemorrhage (IVH) grade >II, Retinopathy of Prematurity (ROP) grade III, Patent Ductus Arteriosus (PDA), nasal trauma, the time of oral feeding initiation, and mortality.

RDS was diagnosed based on clinical and radiological findings. Moreover, BPD was defined based on the national healthcare standards (14). PDA was diagnosed using the routine echocardiography 48-96 hours after birth (15), while IVH was diagnosed using a Cranial ultrasound graded by the Papile grading classification (16). Also, necrotizing enterocolitis was diagnosed using the modified Bell's staging criteria (17) The ROP requiring laser treatment was diagnosed using the criteria by the American Academy of Pediatrics (AAP), American Academy of Ophthalmology (AAO), and American Association for Pediatric Ophthalmology and Strabismus (AAPOS) (18).

2-4. Data Analyses

After data collection, the SPSS 16 software (SPSS Inc., Chicago, IL, USA) was used for data analysis. The quantitative variables were described using the mean and standard deviation, while the qualitative variables were described using the frequency. The Chi-square and Fisher's exact tests were used to analyze the qualitative nominal variables, while the student's t-test and the non-parametric Mann-Whitney test were used for quantitative data comparisons. The significance level was considered at 0.05.

3- RESULTS

A total of 95 preterm neonates undergoing NCPAP (n = 47) or NIPPV (n = 48) as the respiratory support were studied. The groups had no significant difference in demographic and baseline clinical features, including the maternal age, birth weight, 1-minute and 5-minute Apgar scores, gender, maternal underlying disease, intrauterine growth retardation, history of antenatal steroid administration, and the type of delivery (**Table 1**).

Table-1: Comparison of demographic and clinical information of the groups

Variable	NIPPV (N = 48)	NCPAP (N = 47)	P-value
Mother's age,y	25.42±5.79	24.51±5.63	0.442
Gestational age, wk	31.54±2.46	31.51±2.19	0.948
Birth weight,g	1392.70±416.16	1378.51±65.39	0.854
Apgar score at 1 minute	5.81±1.59	6.08±1.38	0.376
Apgar score at 5 minute	7.58±1.16	7.97±1.02	0.367
Male	25 (52.1)	23 (48.9)	0.759
Underlying disease	13 (27.1)	14 (29.8)	0.823
IUGR	3 (6.2)	4 (8.5)	0.714
C-section	30 (62.5)	29 (61.7)	0.936
Antenatal steroids	25 (52.1)	24 (518.1)	0.9212

Preeclampsia: n=19; Diabetes: n=10

Data are reported as number (%) or as mean ± standard deviation

Compared to the NCPAP group, the NIPPV group had a significantly lower rate of endotracheal intubation and invasive mechanical ventilation within 72 hours after birth (8.3% vs. 27.7%, P=0.014); however, the groups were not significantly different in the surfactant doses received (66% vs. 56.2%, P=0.332), the mean respiratory support duration (6.89±3.20 vs. 6.70±3.71 days, P=0.295), the mean hospital stay (19.52±12.364 vs. 17.40±9.57 days, P=0.591), bronchopulmonary dysplasia (4.2% vs. 8.5%, P=0.435), and mortality (6.25% vs. 12.8%, P=0.317) (**Table 2**).

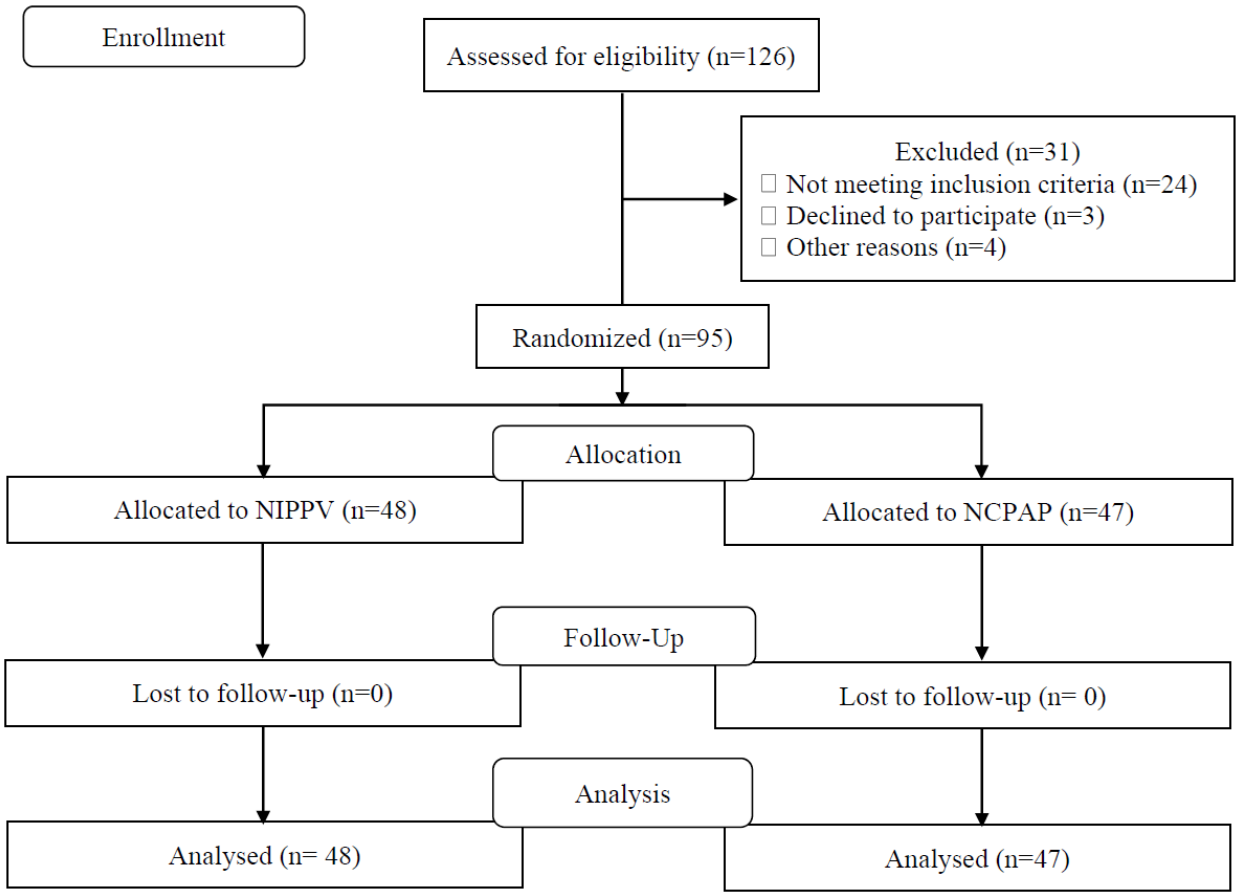

Fig. 1: The flow diagram of the study process

4- DISCUSSION

According to the results of the present study on the neonates treated with LISA, initial respiratory support using the NIPPV could further reduce the need for invasive mechanical ventilation in the first 72 hours after birth, as compared to the NCPAP.

In other words, we found that the rate of non-invasive respiratory support failure, need for endotracheal intubation, and subsequent invasive mechanical ventilation were lower in the NIPPV group than in the NCPAP group. The results of the studies by Shah et al. (13), Mahmoud et al. (19), and Oncel et al. (20) on preterm neonates with RDS were also compatible with our findings, showing a significantly lower rate of need for invasive ventilation in the first 7 days of birth in the NIPPV group than the NCPAP group. This finding is also supported by other studies (7, 12,

21), such as a review and meta-analysis by Lemyre et al. (22) that reported a significantly lower rate of respiratory failure and need for intubation in the NIPPV group compared to the NCPAP group. However, the present study was different from the mentioned study in using the LISA as a treatment. Also, the results of the studies by Skariah et al. (23) and Gharehbaghi et al. (24) were incompatible with ours, reporting that NIPPV could not reduce the need for invasive ventilation.

Table-2: Comparison of primary and secondary outcomes in the groups

Variable			NIPPV (N = 48)	NCPAP (N = 47)	P-value
Primary outcomes	Need to invasive ventilation in the first 72 h of life		4 (8.3)	13 (27.7)	0.014
	Surfactant administration	1st dose	21(43.8)	16(34)	0.332
		2nd dose	27(56.2)	31(66)	
Secondary outcomes	Duration of non-invasive ventilation, d		6.89 ±3.20	6.70 ± 3.71	0.295
	Patent ductus arteriosus		8 (16.7)	12 (25.5)	0.289
	bronchopulmonary dysplasia		2 (4.2)	4 (8.5)	0.435
	Pneumothorax		2 (4.2)	2 (4.3)	1.00
	Intraventricular hemorrhage		3 (6.2)	2 (4.3)	1.00
	Retinopathy of Prematurity		2 (4.2)	1 (2.1)	1.00
	Necrotizing enterocolitis		2 (4.2)	1 (2.1)	1.00
	Pulmonary hemorrhage		2 (4.2)	3 (6.4)	1.677
	Died		3 (6.25)	6 (12.8)	0.317
Other clinical outcomes	Respiratory complications		9 (18.8)	12 (25.2)	0.426
	Severity of nasal trauma		1 (2.1)	4 (8.5)	0.204
	Time of oral feeding, d		4.31 ±1.53	4.02 ±1.33	0.355
	Duration of hospital stay, d		19.52 ±12.36	17.40 ±9.57	0.591

Data are reported as number (%) or as mean ± standard deviation

The rate of respiratory failure is reported to be remarkably high, up to 50%, in the neonates supported by NCPAP (23). The most important causes of neonatal respiratory failure include recurrent apnea episodes, bradycardia, hypoxia, and respiratory acidosis (12). Various mechanisms have been suggested to be involved in the lower rate of respiratory failure in the NIPPV compared to the NCPAP (25). It has been reported that NIPPV can improve the pulmonary mechanics by increasing the Mean Airway Pressure (MAP), decreasing the work of breathing (26), improving the asymmetric thoracoabdominal movements, and decreasing the resistance to flow through the nasal prongs (27).

The superiority of our study to the previous studies (12, 23, 24) was using the novel method of LISA in both groups, which decreased the need for mechanical ventilation and respiratory support duration in comparison to the INSURE method (10, 11, 28, 29). In the studies by Mahmoud et al. (19) and Oncel et al. (20), which were also performed using the LISA, NIPPV had higher effectiveness compared to the NCPAP in reducing the need for the second dose of surfactant. However, our study did not find any significant intergroup difference in the mentioned variable.

We found no intergroup difference in the mean duration of non-invasive respiratory support, which was compatible with the study by Mahmoud et al. (19). The neonatal sequelae were not also different between the groups in our study, which was compatible with the findings by Mahmoud et al. (19), Oncel et al. (20), and Lemyre et al. (22). Moreover, our studies and the mentioned studies did not find a significant intergroup difference in the development of ROP, PDA, pulmonary hemorrhage, BPD, pneumothorax, and the time of oral feeding initiation as well. However, inconsistent with our results, Morley et al. (30) reported a higher rate of necrotizing enterocolitis in the NIPPV group, while an increased risk of pneumothorax in the NCPAP group was observed. Also, an extensive study by Kirpalani et al. (31) showed that no neonatal sequelae could be attributed to one of these nasal respiratory support methods. Eventually, our study found no intergroup difference in mortality and mean hospital stay, which was compatible with the previous studies (13, 19, 20, 22, 31).

A limitation of our study was that it was performed in a single healthcare facility center. However, the strength of our study was comparing different non-invasive respiratory support techniques while using the novel LISA method, which could reduce the risks associated with endotracheal intubation. Also, both initial respiratory support modalities of NCPAP and NIPPV were used immediately after the NICU admission.

5- CONCLUSION

In comparison to the NCPAP, NIPPV could significantly reduce the need for mechanical ventilation in the first 72 hours after birth in the preterm neonates with 28 to 36 weeks of age suffering from RDS who are treated with LISA. However, it did not affect the development of severe sequelae, mortality, respiratory support duration, length of hospital stay, and the time of oral feeding initiation.

6- ETHICAL CONSIDERATIONS

The present study was approved by the Research Ethics Committee of Hamadan University of Medical Sciences with the approval code of IR.UMSHA.REC.1398.866. Moreover, it was registered in the clinical trial registration center with the registration code of IRCT20151123025202N9.

The parents of the neonates were provided with sufficient explanations on the study objectives and gave informed consent if willing to participate**.**

7- CONFLICT OF INTEREST

None

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