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Effectiveness of Nasal Intermittent Positive Pressure Ventilation versus Nasal Continuous Positive Airway Pressure in Preterm Infants after Less Invasive Surfactant Administration

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Abstract

Background

Non-invasive ventilation is increased used in preterm infants. We aimed to compare the effectiveness of nasal intermittent positive pressure ventilation (nIPPV) versus nasal continuous positive airway pressure (nCPAP) in preterm infants with respiratory distress syndrome (RDS) after less invasive surfactant administration (LISA).

Materials and Methods

In this clinical trial, eighty two preterm infants admitted in neonatal intensive care unit, Sohag University Hospital, Egypt with a gestational age of 28–34 weeks, mean ± standard deviation birth weight (1259.44±377.22 grams), suffering from RDS but not requiring intubation in the delivery room were included in the study. Forty one received nIPPV as an initial respiratory support (RS). If nIPPV failed, surfactant administration was given with the LISA approach and patients continued on nIPPV. This group was compared with a historical cohort group of 41 infants managed with nCPAP as an initial RS, and if nCPAP failed, the surfactant was given by LISA.

Results

There was no significant difference between the case and control group regarding the mean ± SD gestational age or birth weight. When nIPPV was used as the primary RS in preterm infants with RDS compared to nCPAP, it had a significantly less nIPPV failure (31.71% versus 53.66%, P = 0.04), had significantly fewer infants who needed invasive ventilation within the first seven days of life (12.20% versus 34.14%, P = 0.03), and the total days of supplemental oxygen was less (9 (3–18) days versus 12 (6–34) days, P = 0.02).

Conclusion

In infants born at 28–34 weeks gestation, nIPPV, when used as the primary RS, reduced the need for invasive ventilation and the surfactant requirement within the LISA technique.

Key Words: Infants, Non-invasive Ventilation, Premature, Surfactant.

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1- INTRODUCTION

The main strategy to manage respiratory distress syndrome (RDS) in preterm infants depends on the application of non-invasive ventilatory support, primarily, nasal continuous positive airway pressure (nCPAP) (1). Compared to primary intubation and mechanical ventilation (MV), primary nCPAP decreases the combined risk of bronchopulmonary dysplasia (BPD), or death (2, 3). However, the failure rate of the nCPAP approach remains high, with 65% of severely preterm infants requiring secondary MV and 50% requiring surfactant therapy (4). Nasal intermittent positive pressure ventilation (nIPPV) may have a beneficial effect over nCPAP by delivering ventilator breaths via nasal prongs. It is known from research that the use of nIPPV is associated with both decreasing respiratory failure and the need for re-intubation and MV (5, 6).

However, Kirpalani et al. (7) found that the rate of survival without BPD did not differ significantly after non-invasive respiratory support with nIPPV, as compared with nCPAP. After a meta-analysis of trials indicated that early nCPAP combined with the beneficial effects of a surfactant significantly reduced the need for ventilation and subsequent BPD, a combination of these methods, called an intubation, surfactant and extubation (INSURE) method, was propagated and has since been widely used (8). However, this method also requires intubation for surfactant administration and positive pressure ventilation, even for a short time, which is enough to initiate significant lung injury (9). Recently, minimally or less invasive surfactant administration (MISA or LISA) have come into use in neonatal practice (10). Some clinical trials have reported that the LISA during nCPAP reduced the need for MV and reduces the risk of BPD in preterm infants (10, 11). Ramanathan et al. (12) showed the benefits of nIPPV compared with nCPAP within the INSURE approach. Oncel et al. (13) in a randomised controlled trial study showed the benefits of nIPPV compared with nCPAP within the LISA technique. They emphasised the need for further studies comparing nIPPV and nCPAP using the LISA technique in different gestational age groups. However, the results remain confusing regarding the benefits of the use of nIPPV over nCPAP as an initial respiratory therapy in preterm infants (7). Therefore, the aim of this study was to compare nIPPV and nCPAP as the initial respiratory support in preterm infants with RDS. Furthermore, surfactant therapy was given if indicated by LISA technique via a small catheter tube placed in the trachea while these infants continue on nIPPV or nCPAP.

2- MATERIALS AND METHODS

2-1. Patients selection

In this clinical trial (with registration number-ID: TCTR20180905004), forty one preterm infants with a gestational age of 28–34 weeks suffering from RDS were included in the study, if admitted to the neonatal intensive care unit (NICU) of Sohag University Hospital, Egypt, during one year from January 2017 until December 2017. They received prospectively a nIPPV as an initial respiratory support. If nIPPV failed, surfactant administration was given with the LISA approach and patients continued on nIPPV (nIPPV group). This group was compared with a historical cohort group (during 2016 year) of 41 infants managed in our NICU with nCPAP as an initial respiratory support, and if nCPAP failure occurred, the surfactant was given by the LISA approach and patients continued on nCPAP (nCPAP group). Both nCPAP and nIPPV were delivered by a neonatal ventilator Babylog 8000 plus (Drager Inc, Lubeck, Germany) via short, bi-nasal prongs connected to Y-piece after removal

of the flow sensor. During the study period, the LISA protocols, the staffing, patient monitoring, training and care protocols were the same between both prospective and historical cohort groups. RDS was diagnosed in these children if they had, cyanosis, tachypnea more than 60 breath/minutes, and grunting, intercostal, subcostal retractions, and was confirmed by typical X-ray finding of RDS as a ground glass appearance, reticulogranular shadow or air bronchogram, metabolic acidosis and hypoxemia in blood gases. Ethical approval for the study and the investigation were obtained from the Research Committee of Medical Faculty at Sohag University, Egypt, and written informed consent was obtained from all parents of the study group. Infants with major congenital anomalies, no parental written informed consent, and who required early intubation according to the American Academy of Pediatrics guidelines for neonatal resuscitation (14) more than 34 weeks or less than 28 weeks, were excluded from the study.

2-2. Study protocol

All included preterm infants were resuscitated in a delivery room by a built in T-device (Drager Hill-Rom Air Shields resuscitator, Lubeck, Germany), and stabilised in the NICU according to our standard neonatal protocol. In NICU, all preterm infants met the inclusion criteria, put under nIPPV in non-synchronised mode [rate 20–40 breaths/minute, peak inspiratory pressure (PIP) 15–25 cm Hg, positive end expiatory pressure (PEEP) 4–6 cm Hg, fraction of inspired oxygen (FiO2) 0.21 up to 0.4]. The advantage of this mode is that it supports baby breathing during inspiration by PIP and during expiration by PEEP; nIPPV failure occurred when any child under nIPPV and needing FiO2 more than 0.4 to maintain SpO2 levels between 85%, and 92% (measured via a pulse oximeter), or had intractable apnea, had PCO2 >60 mmHg, had severe respiratory distress with retractions, and/or reached the maximum allowed nIPPV setting as described above. Under non-invasive ventilation, the surfactant was administered as a rescue therapy. LISA was achieved using the Hobart method for instillation of the surfactant via a 5F rigid sterile arterial umbilical catheter without using Magill forceps (15). The catheter was placed between the vocal cords under visualisations by a laryngoscope. The laryngoscope was removed and the catheter left in place. Survanta (Abbott Laboratories, North Chicago, IL, USA) at a dose of 100 mg/kg (4 mL/kg) was administered in a bolus over 1–2 min in the tracheal catheter, and then the catheter was immediately removed.

No pre-medication was used, such as sedation or atropine. After administration of the surfactant by LISA, preterm infants continued with nIPPV on the same previous setting. The historical cohort control group (nCPAP group), was comprised of forty one preterm infants with a gestational age of 28–34 weeks suffering from RDS who were admitted to our NICU, during one year from January 2016 until December 2016. They received nCPAP as an initial respiratory support (PEEP 4-6 cm Hg and FiO_2 from 0.21 to 0.4). nCPAP failure occurred when any child under nCPAP and needing FiO2 more than 0.4 to maintain SpO2 levels between 85% and 92%, or had intractable apnea, had PCO2 > 60 mmHg, had severe respiratory distress with retractions, and/or reached the maximum allowed nCPAP setting as described above, then surfactant administration was given with the LISA approach, as described previously and patients continued on nCPAP (nCPAP group). Failure of LISA in both groups was considered when the infants received one dose of surfactant by the LISA approach and reached the maximum

allowed respiratory support settings on nCPAP (PEEP > 6 cm Hg and FiO_2 > 0.4) and on nIPPV (rate >40 breaths/minute, PIP > 25 cm Hg, PEEP > 6 cm Hg, FiO2 > 0.4). Additionally, if infants showed persistent hypoxemia (SPO2 less than 85%), partial pressure of carbon dioxide more than 60 mm Hg or metabolic acidosis (PH < 7.20), repeated episodes of apnea and bradycardia requiring positive pressure ventilation by Ambu bag or T-device, severe respiratory distress, pulmonary haemorrhage or cardiopulmonary arrest without effective resuscitation, they were intubated and mechanically ventilated by a Babylog 8000 plus ventilator and another dose of surfactant was given if clinically indicated. After extubation, the initial mode of nasal support (nIPPV or nCPAP) was continued until the patient was weaned to room air or nasal cannula. Infants supported with nCPAP were not allowed to be switched to nIPPV, even when the severity of their respiratory symptoms increased. Furthermore, we did a complete clinical neonatal examination, with the full history taken for prenatal, perinatal and postnatal risk factors and patient progress recorded, such as gestational age, birth weight, gender, Apgar score at 1 and 5 min, premature rupture of membranes, antenatal steroid course, number of doses of surfactant courses, needed MV, nCPAP or nIPPV failure, total duration of MV, duration to full enteral feeding, degree of Necrotising enterocolitis (NEC), if present, grades of Intraventricular hemorrhage, pneumothorax, total duration of hospital stay, neonatal outcome, BPD, retinopathy of prematurity and other complications of prematurity and mortality.

2-3. Statistical analysis

Data were analysed using STATA intercooled version 14.2. Quantitative data were represented either as the mean, standard deviation (SD), or median, interquartile range. Data were analysed using the student t-test to compare the means of two groups. When the data was not normally distributed, the Mann-Whitney test was used. Quantitative data was presented as the number and percentage and compared using either the Chi square test or Fisher exact test. The P-value was considered significant if it was less than 0.05.

3- RESULTS

Of the 82 new-borns with RDS who were enrolled in the study, 41 (50%) patients were initially treated with nIPPV (case group) and 41 patients (50%) with nCPAP (control group). Within the study groups, there was no statistically significant difference between the case and control group regarding the mean ± SD gestational age (30.29±1.83 weeks and 30.34±1.51 weeks, respectively, P= 0.90), mean ± SD birth weight (1259.02±327.41 grams and 1276.59±348.32grams, respectively, P = 0.81). One full course of antenatal steroids was administered to 90.24% of the nIPPV group versus 85.37% in the nCPAP group (P=0.66). Furthermore, other patients' demographic and clinical characteristics were not different between the groups, as shown in **Table.1**. As shown in **Table.2**, when nIPPV was used as the primary respiratory support in preterm infants with RDS compared to nCPAP, it had a significantly less nIPPV failure (31.71% patients versus 53.66% patients, P= 0.04), significantly fewer infants who needed invasive ventilation with the first seven days of life (12.20% patients versus 34.14% patients, P= 0.03), the number of surfactant doses were decreased (17 (41.6%) patients (13 patients by LISA plus 4 patients another surfactant dose after MV) versus 33 (80.4%) patients (22 patients by LISA plus 11 patients another surfactant dose after MV, P= 0.04) and the total days of supplemental oxygen was reduced 9 (5-15) days versus 12 (8-17) days, P= 0.02). However, there were no statistically

significant differences between the nIPPV and nCPAP groups regarding the rate of BPD, pneumothorax, Patent ductus arteriosus (PDA), intraventricular haemorrhage, pulmonary haemorrhage, necrotising enterocolitis ≥ stage II and retinopathy of prematurity. Furthermore, the use of nIPPV was not superior to nCPAP at the time to reach full enteral feeding, the total duration of hospitalisation or even the mortality rates (all P values > 0.05, as shown in **Table.2**).

When comparing nIPPV versus the nCPAP subgroup of less than or equal to 30 weeks of gestational age. The nIPPV group required significantly less surfactant dosing, less need for MV and significantly fewer days of supplemental oxygen (P = 0.03, 0.05 and 0.03, respectively). However, there were no other significant differences between both these subgroups for neonatal morbidity or mortality, as described in **Table.3**.

Table-1: Patients characteristic of study groups.

Variables	nIPPV, n=41	nCPAP, n=41	P-value
Gestational age, week	30.29±1.83	30.34±1.51	0.90
Male	20 (48.78%)	26 (63.41%)	0.18
CS	31 (75.61%)	25 (60.98%)	0.15
Birth weight, gram	1259.02±327.41	1276.59±348.32	0.81
Maternal age, year	27.53±5.67	27.8±5.93	0.79
Antenatal steroid course	37 (90.24%)	35 (85.37%)	0.66
PROM>18 hours	13 (31.71%)	15 (36.59%)	0.64
Preeclampsia	10 (24.39%)	11 (26.41%)	0.82
Multiple pregnancies	9 (21.95%)	12 (29.41%)	0.35
APGAR score 1, Minute	5 (4-7)	5 (4-6)	0.86
APGAR score 5, Minute	8 (6-9)	7 (5-9)	0.39

Mean ± SD, rate (%), or median and interquartile range. nIPPV; nasal intermittent positive pressure ventilation; nCPAP: nasal continues positive airway pressure; CS: Cesarean section; PROM: premature rupture of membrane.

Table-2: Neonatal outcomes of all studied patients.

Variables	nIPPV, n=41	nCPAP, n=41	P- value
Duration of nCPAP/nIPPV, day	7 (5-10)	7 (5-11)	0.65
Failure nCPAP/nIPPV and required Surfactant by LISA	13 (31.71%)	22 (53.66%)	0.04
Time for failure of nCPAP/nIPPV and required surfactant, hours	8 (6-12)	5 (4-8)	0.03
Failure LISA and required MV (Need for invasive ventilation)	5 (12.20%)	14 (34.14%)	0.03
Duration of MV, day	3 (3-4)	7 (2-10)	0.25
Duration of supplemental oxygen, day	9 (5-15)	12 (8-17)	0.02
Pneumothorax	2 (4.88%)	2 (4.88%)	1.00
Bronchopulmonary dysplasia	2 (4.88%)	2 (4.88%)	1.00
Died	2 (4.88%)	4 (9.76%)	0.68
Required 2 dose of surfactant	4 (9.76%)	11 (26.83%)	0.04
Patent ductus arteriosus medication	9 (21.95%)	9 (21.95%)	1.00
Pulmonary hemorrhage	4 (9.76%)	4 (9.76%)	1.00
Retinopathy of prematurity	1 (2.43)	1(2.43)	1.00
Necrotizing enterocolitis ≥ stage II	3 (7.32%)	4 (9.76%)	1.00
Intra ventricular hemorrhage	3 (7.32%)	3 (7.32%)	1.00
Time to full feed, day	8 (8-10)	8 (7-10)	0.20
Total duration of hospitalization, day	16 (12-22)	16 (14-24)	0.43

Mean ± SD, rate (%), or median and interquartile range. nIPPV: nasal intermittent positive pressure ventilation; nCPAP: nasal continues positive airway pressure; LISA: less invasive surfactant application; MV: mechanical ventilation.

Table-3: Neonatal outcomes of in patients less than or equal to 30 weeks of gestational age.

Variables	nIPPV n=15	nCPAP n=14	P- value
Duration of nCPAP/nIPPV, day	12 (10-15)	12 (10-15)	0.86
Failure nCPAP/nIPPV and required Surfactant by LISA	5 (33.33%)	9 (64.29%)	0.03
Time for failure of nCPAP/nIPPV and required surfactant, hours	9 (6-15)	4 (4-6)	0.01
Failure LISA and required MV (Need for invasive ventilation)	3 (20.00%)	6 (42.85%)	0.05
Duration of MV, day	3.5 (3-4)	8 (4-10)	0.16
Duration of supplemental oxygen, day	15 (15-18)	20 (15-24)	0.03
Pneumothorax	0	2 (14.29%)	0.22
Bronchopulmonary dysplasia	2 (13.33%)	2 (14.29%)	1.00
Died	2 (13.33%)	4 (28.57%)	0.39
Required 2 dose of surfactant	1 (6.66%)	4(28.57%)	0.02
Patent ductus arteriosus medication	9 (60.00%)	9 (64.29%)	0.81
Pulmonary hemorrhage	4 (26.67%)	4 (28.57%)	1.00
Retinopathy of prematurity	1 (6.66)	1 (7.14)	1.00
Necrotizing enterocolitis ≥ stage II	3 (20.00%)	4 (28.57%)	0.59
Intra ventricular hemorrhage	3 (20.00%)	3 (21.43%)	0.92
Time to full feed, day	10 (8-18)	11 (9-15)	1.00
Total duration of hospitalization, day	24 (20-30)	25 (24-30)	0.35

Mean ± SD, rate (%), or median and interquartile range. nIPPV: nasal intermittent positive pressure ventilation; nCPAP: nasal continues positive airway pressure; LISA: less invasive surfactant application; MV: mechanical ventilation.

4- DISCUSSION

The aim of this study was to compare nIPPV and nCPAP as the initial respiratory support in preterm infants with RDS and after LISA. The main results were, among premature infants with RDS, the use of nIPPV, compared to nCPAP as an initial respiratory support, had a significantly better non-invasive respiratory support outcome with only 31.71% of the patients having nIPPV failure compared to 53.66% of the patients having nCPAP failure. Furthermore, in this study we gave the surfactant by the LISA approach for infants whom failed nIPPV or nCPAP. The use of LISA within nIPPV significantly decreased the need for invasive ventilation within the first seven days of life, reduced the surfactant requirement and required fewer days of supplemental oxygen. However, the rate of BPD, total durations hospital stay, time to reach full enteral feeding and other neonatal morbidity or mortality were not statistically significant different between the two groups. The use of CPAP for the treatment of new-born with respiratory distress was first described by Gregory et al. in 1971 (16). Since that time, many prospective studies have shown an improved survival of premature infants treated with early CPAP (17). However, the failure of CPAP may be as high as 60%, depending on gestational age, birth weight, disease severity and other perinatal variables (7, 18). These failures were improved with the use of nIPPV as a primary respiratory support in which only 30% of patients failed nIPPV and needed MV in Silveira et al. clinical trial (18). Since the avoidance of BPD seems to be an important long-term advantage for preterm infants, many authors have also compared non-invasive ventilation methods in terms of BPD development; nIPPV is considered as a strengthened version of nCPAP with increased flow delivery in the upper airway, increased minute volume, functional residual capacity and

recruitment of collapsed alveoli (19, 20). Some clinical studies in preterm infants receiving nIPPV as primary respiratory support compared to nCPAP had reduced the need for MV in the first week, as well as the duration of MV (12, 21, 22) and in one study decrease incidences of BPD (12). Contrary to our results, Chen et al. (23), in a randomised clinical trial in preterm twin neonates with RDS, they found that the rates of invasive ventilation did not differ significantly between the nIPPV and nCPAP groups (11.9% versus 19.6%, P = 0.080). Furthermore, there was also other research not in agreement with our results regarding the superiority of nIPPV over nCPAP in this issue (7, 24). To reduce ventilator-induced lung injuries from invasive MV (25-27), Verder et al. in 1994 (8) firstly introduced the concept of the INSURE technique. Nowadays, INSURE is a widely accepted technique (8, 28). However BPD incidences with INSURE still not markedly reduced in preterm infants, as even a few manual breaths were sufficient to cause irreversible pulmonary damages (9).

The surfactant in spontaneous breathing infants under CPAP (LISA) allows the advantage of surfactant and avoidance of MVs. Lau et al. (29) in a recent meta-analysis in 2017 found that LISA significantly reduced the need and durations of MV, the duration of supplemental oxygen and a non-significant trend toward a reduction in the incidence of BPD. Furthermore, Aldana-Aguirre et al. (30) carried out another meta-analysis in which six clinical trials were identified, enrolling a total of 895 infants comparing LISA versus INSURE, or prolonged MV. The use of the LISA technique significantly reduced BPD at 36 weeks, and the need for MV within 72 hours of birth. However, there were no differences noted for the outcome of death and other neonatal morbidities. In our study, we used only the LISA technique and the need for MV after LISA occurred only in 12.20% in the nIPPV group and 34.14% in the nCPAP group (P = 0.03). In our study, nIPPV was better than nCPAP at reducing the need for invasive ventilation and surfactant requirements. Our findings suggest that the combination of LISA and nIPPV support is effective in achieving favourable outcomes, such as those reported by Oncel et al. (13) in a randomised controlled trial study that showed the benefits of nIPPV compared with nCPAP within the LISA approach. They found that the nIPPV group required less surfactant therapy and less need for MVs in the first 72 hours of life. However, they found that the accompanied nIPPV and LISA reduce the incidence of BPD in preterm infants more than 30 weeks only. This does not agree with our results, as we found no statistically significant difference in the incidences of BPD, other neonatal morbidity or mortality in any gestational age of the studied groups. This study has some limitations. First, the study was not blind, which could have resulted in biased decisions regarding initiating MV. Second, it was a single-centre study.

We attempted to minimise the potential impact of this possibility by completing the study during the nIPPV group prospectively and retrospectively compared with nCPAP group by using strict criteria for initiating MVs and surfactant therapy by LISA technique in both groups. Third, in this study, we include only preterm infants from 28–34 weeks gestational age and did not include infants born at very early gestational ages, in which the adverse effects of MVs are common and serious. We exclude these infants, as in our study centre, at the earliest gestational ages (23–27 weeks), mortality rates are extremely high and intensive care is not universally provided. Therefore, we cannot extrapolate the results of this study to infants with gestational ages of less than 28 weeks.

Finally, although we did not find complication differences in neonatal morbidity and mortality between nCPAP and nIPPV in our study groups, it is possible that our numbers of patients was not large enough to identify them. Future clinical trials should be carried out to address this concern. Our study has some strong implications. First, it is compare different non-invasive respiratory support with LISA approach, so that the risks associated with endotracheal intubation were avoided. Second, both nCPAP and nIPPV modes were applied immediately on NICU admission as initial respiratory support.

5- CONCLUSION

In conclusion, nIPPV had positive results over nCPAP as the primary respiratory support in preterm infants with RDS and reduced the need for MV. Furthermore, the use of LISA within nIPPV significantly decreased the need for invasive ventilation within the first seven days of life, reduced the surfactant requirement, and had fewer days of supplemental oxygen. However, larger and well-designed randomised controlled trials, especially in extremely preterm infants, are needed using the LISA approach within different non-invasive respiratory support.

6- AUTHORS CONTRIBUTIONS

MRA conceived, designed, performed the investigations, wrote and final approved the manuscript. All our neonatology unit team (nurses, residents and specialists) take apart in monitoring and follow up of the patients during the study period.

7- ABBREVIATIONS

BPD: Bronchpulmonay dysplasia,
FiO2: Fraction of inspired oxygen,
INSURE: Intubation-surfactant-Extubation,
LISA: Less invasive surfactant administration,
MV: Mechanical ventilation,
nCPAP: Nasal continues airway pressure,
PCO2: Partial pressure of carbon dioxide,
PEEP: Positive end expiatory pressure,
PIP: Peak inspiratory pressure,
RDS: Respiratory distress syndrome,
SpO2: Oxygen saturation,
nIPPV: Nasal intermittent positive pressure ventilation.

8- CONFLICT OF INTEREST: None.

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