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Evaluation of the efficacy of nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) in the preterm babies with respiratory distress syndrome (RDS)

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Abstract: *Background*: Neonatal respiratory distress syndrome (RDS), is an acute lung disease caused by pulmonary surfactant deficiency. RDS is generally due to lung immaturity leading to surfactant deficiency in alveoli of lungs and subsequent collapse during expiration. CPAP overcomes this with application of continuous distending pressure through breathing cycle in spontaneously breathing neonate. Recently NIPPV was supposed to be better modality of treatment for such neonates with RDS. However there is paucity of literature regarding the efficacy of NIPPV versus nasal CPAP in the management of preterm babies with RDS. *Objectives*: Present study aimed to evaluate the efficacy of NIPPV versus NCPAP in the preterm babies < 34 weeks of gestation. *Material & Methods*: This study was conducted in the Neonatal Intensive Care Unit of SKIMS from April 2016 to April 2017. Data was analyzed using SPSS.A total of 89 preterm infants less than 34 weeks of gestational age were enrolled in the study over a period of 12 months. Forty nine received NCPAP and forty were in the NIPPV group. *Results*: Average length of stay in the NICU in NCPAP group was 13.96 ± 6.57 days while as it was 10.85 ± 7.26 days in NIPPV group and the difference was statistically significant (p = 0.037). The mortality was 8.16% (4/49) patients in the NCPAP group and 2.50% (1/40) in the NIPPV group died and the difference was statistically insignificant (p = 0.25). *Conclusions:* NIPPV not only decreases the need for mechanical ventilation in the first 72 of hours of life in preterm babies but also decreases the duration of NICU and hospital stay and decreases the need for surfactant replacement therapy.

Keywords: Nasal Intermittent Positive Pressure Ventilation, Nasal Continuous Positive Airway Pressure, Respiratory Distress Syndrome.

Introduction

Respiratory distress syndrome (RDS) also called Neonatal respiratory distress syndrome, is an acute lung disease caused by pulmonary surfactant deficiency [1-2]. It is caused by developmental insufficiency of surfactant production or structural immaturity in lungs [2]. It can also result from a genetic problem with the production of surfactant associated protein [3]. As RDS is generally due to lung immaturity, the best intervention would be to prevent premature birth [4]. As premature birth cannot be avoided, RDS may be prevented or its severity reduced by taking timely interventions [5]. Surfactant deficiency is the primary cause of RDS. Endogenous surfactant is a biochemical compound composed of phospholipids (phosphatidyl choline, phosphatidyl glycerol), neutral lipids (cholesterol) and proteins (apoproteins-surfactant protein SP-A, SP-B, SP-C, SP-D) [6-7].

Surfactant is secreted by type II pneumocytes and functions to reduce lung collapse during end expiration by decreasing surface tension within the terminal airways and alveoli [8]. Exogenous lung surfactant is either natural or synthetic [8]. Natural surfactant is extracted from animal sources such as bovine or porcine synthetic surfactant is manufactured from

compounds that mimic natural surfactant properties natural surfactant have been found to be more desirable choice [8-9]. Delivery techniques include (a) standard technique of incubation, surfactant administration and continuing mechanical ventilation or (b) INSURE technique (Intubation-surfactant-extubation) which includes early surfactant replacement therapy with prompt extubation to nasal continuous positive airway pressure (NCPAP) [10]. This technique is associated with less need for mechanical ventilation, lower incidence of BPD and fewer air leak syndromes, when compared to later selective surfactant replacement therapy, mechanical ventilation and extubation from lower ventilation settings [11-12].

NCPAP is the application of continuous distending pressure throughout the respiratory cycle in spontaneously breathing infant [13]. Nasal intermittent positive pressure ventilation (NIPPV) involves giving CPAP to the infant in the intermittent mandatory ventilation (IMV) mode through a nasal or nasopharyngeal interface device [13]. NIPPV offers the main physiologic advantage of CPAP (stabilization of alveoli by positive airway pressure) and theoretically promotes better ventilation by delivering positive pressure breaths to the lower airways [13-14].

NIPPV is supposed to be better modality of treatment for babies with RDS [15-17]. However there is paucity of literature regarding the efficacy of nasal NIPPV versus nasal CPAP in the management of preterm babies with RDS [17]. We therefore decided to evaluate the efficacy of NIPPV versus NCPAP in the preterm babies < 34 weeks of gestation.

Material and Methods

This study was conducted in the Neonatal Intensive Care Unit (NICU) of Sheri-Kashmir Institute of Medical Sciences (SKIMS) Soura, a tertiary care hospital in northern India from April 2015 to April 2016. This study was conducted after taking institutional ethical clearance from the ethics committee of Sheri-Kashmir Institute of Medical Sciences (SKIMS), Soura (Ref. no. SIMS 1 131/IEC-SKIMS/2016-140, dated April 04th, 2016; recommended on 14/03/15). This was a prospective observational study where preterm infants < 34 weeks with diagnosis of RDS were assigned to NIPPV or NCPAP depending on the availability of the device. If both the devices were available at the time of allocation, the infant was allocated to NCPAP.

Inclusion Criteria:

Preterm infants less than 34 weeks were included in the study. RDS was diagnosed as per the NNF definition (classical symptoms such as need for O_2 supplementation, tachypnea, intercostals retractions, and grunting and exclusion of other causes of respiratory failure supplemented by typical radiographic pattern with reduced air content and a reticulogranular pattern of lung and air bronchograms). Gestational age was calculated by prenatal USG, EDD, LMP and new Ballard score [19].

Exclusion Criteria:

Infants with following conditions were excluded:

- Structural cyanotic CHD
- Severe congenital malformations including CDH, TEF, cleft lip, and palate
- Pulmonary hypoplasia
- Pneumothorax

In the NCPAP group, surfactant (Neosurf) 100 mg/kg/dose was administered via a thin ETT catheter by INSURE technique followed by extubation to NCPAP. NCPAP was given by Fisher and Paykel Nasal CPAP (BC161, New Zealand, UK) which includes a source of gas flow (6-8L/min), an air oxygen blender (Biomed Devices Blender, USA), humidifier (MR410, Fisher & Paykel Health Care, New Zealand), a respiratory circuit and expiratory hose inserted in a bottle of water. CPAP level delivered is equivalent to the distance that the distal end of expiratory tubing is under water (when sub merged to 5 cm of water gives a CPAP of 5 cm of water). Subjects in the CPAP group were initiated on 5 cm of water and flow 6-7 litres/min. The maximum permissible settings were CPAP 7 cm and fraction of inspired oxygen (FiO2) 0.7. Targeted saturation was 91–93%.

The babies in the NIPPV group were directly started on NIPPV and surfactant was administered if they fulfilled criteria of failure. NIPPV was provided with Maquet

Servo-I infant ventilator via nasal prongs to ventilator circuit. Subjects in NIPPV group were initiated on: frequency 50 / min, peak inspiratory pressure (PIP) 15-16 cm of water, peak end expiratory pressure (PEEP) 5 cm of water, inspiratory time (Ti) 0.3-0.35 sec and flow: 6-7 litres / min. In neonates weighing 1000 g the maximum permissible PIP was 24, while in those >1000 g it was 26 cm. The maximum permissible PEEP was 6 cm of water and frequency 60 per min. Settings in both groups were adjusted based on arterial blood gases (ABG) and clinical parameters. Those patients who needed >40% oxygen, or developed hemodynamic instability or needed intubation in the first 48 hours in the NIPPV group were given surfactant followed by mechanical ventilation.

Subjects were weaned from NIPPV and NCPAP according to following strategy.

a) Absence of respiratory distress (RR < 60 with minimal or no reaction).
b) SpO_2>90% on FiO_2<0.3.
c) CPAP<4cm water.

Sample Size Calculation: Based on our experience, 40% of neonates started on CPAP need endotracheal mechanical ventilation within 72 hours. A sample size of 85 was required to detect a 30% absolute reduction in the need for intubation in the 'early-NIPPV' group, with an alpha error of 5% and power of 80%.

Statistical Analysis: Quantitative data were extracted as mean ± standard deviation (SD) and proportions/percentages as appropriate. Student's t test was used for continuous variables and categorical data was analyzed by chi- square test. Statistical analyses were performed by using SPSS software for windows v16.0, SPSS. P value less than 0.05 was considered statistically significant. In addition statistician was blind to the groups. Dependent variables such as duration of hospitalization, mortality rate, complications of treatment including pneumothorax and ventilator dependency were considered as the efficacy of treatment.

Results

A total of 89 preterm infants less than 34 weeks of gestational age were enrolled in the study over a period of 12 months. Forty nine received NCPAP and forty were in the NIPPV group [Table 1]. The mean post-natal age at admission was 2.04 hours in NCPAP group whereas it was 2.84 hours in the NIPPV group and the difference was statistically insignificant (p=0.066)[Table 1].

In the present study 46.94% (23/49) of neonates in the NCPAP group were males and 53.06% (26/49) were females. In the NIPPV group 55% (22/40) were males and 45% (18/40) were females [Table 1].The mean gestational age in the NCPAP group was 29.90±1.26 whereas the mean gestational age in NIPP group was 30.03±1.33 and the difference was statistically insignificant (p=0.648)[Table 1].The mean birth weight of neonates in the NCPAP group was 1641.43± 320.99 grams while mean birth weight in the NIPP group was 1527.25± 267.68 grams and the difference was statistically insignificant (p=0.071) [Table 1].

Table-1: Demographic details

Variables		Mean ± Standard deviation		p-value
		CPAP (n=49)	NIPPV (n=40)	
Post-natal age (hours)		2.04 ± 1.11	2.04 ± 1.11	0.066
Sex distribution	Male	23 (46.94%)	22 (55.0%)	0.254
	Female	26 (53.06%)	18 (45.0%)	
Gestational age (weeks) of patients		29.90 ± 1.26	30.03 ± 1.33	0.648
Birth weight (g) of patients		1641.43 ± 320.99	1527.25 ± 267.68	0.071
APGAR Score		7.61± 0.73	7.53± 0.72	0.572
DOWNE Score		4.57± 0.68	4.85± 0.70	0.062
CRIB Score		2.80±1.08	3.30± 1.44	0.071

p value < 0.05, considered as statistical significant. p value < 0.001, considered as highly significant.
APGAR score- Appearance, Pulse, Grimace, Activity and Respiration. DS- DOWNE Score
CRIB Score- Clinical Risk Index for Babies

The mean Apgar score at 5 mins of birth for neonates in the NCPAP group was 7.61± 0.73 and 7.53± 0.72 for neonates in the NIPPV group and the difference was statistically insignificant (p=0.572) [Table 1].At admission the mean Downe's score of neonates in the NCPAP group was 4.57±0.68 vs. 4.85± 0.70 for neonates in the NIPPV group and the difference was statistically insignificant (p=0.062) [Table 1].Neonates in the NCPAP group had a mean CRIB score of 2.80±1.08 while neonates in the NIPPV group had a mean CRIB score of 3.30± 1.44 and the difference was statistically insignificant [Table 1].

In the NCPAP group 24.5% (12/49) of neonates were born by cesarean section whereas 15% (6/40) of neonates in NIPPV group were born by cesarean section. In the NCPAP group 75.5% (37/49) were born by vaginal delivery whereas 85% (34/40) of neonates in NIPPV group were born by vaginal delivery. Overall 20.22% of neonates were born by cesarean section whereas 79.77% were born by vaginal route and the difference was statistically insignificant (p=0.091) [Table 2]. All 49/49 (100%) in the NCPAP group received surfactant at admission vs. 20/40 (50%) patients in the NIPPV which was statistically significant (p = 0.05). Four (8.16%) patients in the NCPAP group needed 2nd dose of surfactant vs. 2 patients (5%) in the NIPPV group which was statistically insignificant (p = 0.371) [Table 2].

Table-2: Mode of delivery, surfactant replacement therapy, need for mechanical ventilation (failure of primary modality of treatment), incidence of BPD, combined incidence of BPD and death in the two groups of patients

Outcomes	Category	CPAP		NIPPV		p-value
		(n=49)	%	(n=40)	%	
Mode of delivery	Cesarean section	12	24.4	06	15.0	0.091
	Vaginal delivery	37	75.5	34	85.0	
Surfactant replacement therapy	1st dose	49	100	20	50.0	0.050
	2nd Dose	04	8.1	02	5.0	0.371
Mechanical vent. At 72 hrs.	Yes	11	22.5	0	7.5	0.050
	No	38	77.5	37	92.5	
Overall mechanically ventilated	Yes	18	36.7	07	17.5	0.042
	No	31	63.3	33	82.5	
BPD	Yes	07	14.2	01	2.5	0.050
	No	42	85.8	39	97.5	
BPD and death	Yes	11	22.4	02	5.0	0.023
	No	38	77.5	38	95.0	
Death	Yes	04	8.16	01	2.5	0.251
	No	45	91.8	39	97.5	

11 out of 49 patients (22.5%) in the NCPAP group needed mechanical ventilation at 72 hour of life while 3 out of 40 patients (7.50%) in the NIPPV group needed mechanical ventilation at 72 hour of life and the difference was statistically significant (p=0.05,OR=0.28,CI=0.07-1.08).

Overall 36.7% (18/49) patients in the NCPAP group and 17.50% (7/40) patients in the NIPPV group needed mechanical ventilation and the difference was statistically significant (p=0.04,OR=0.36,CI=0.13-0.99) [Table 2]. Around 14.2% (7/49) patients in NCPAP group developed bronchopulmonary dysplasia vs. 2.5% (1/40) in NIPPV group at 36 weeks of postmenstrual age and the difference was statistically significant (p = 0.050, OR = 0.15, 95% CI=0.01-1.30). The combined incidence

of BPD and death in the NCPAP group was 22.4% (11/49) vs 5% (2/40) which was statistically significant (p = 0.02, OR = 0.18, 95% CI = 0.03-0.87) [Table 2].

Mean duration of mechanical ventilation in the NCPAP group was 1.01± 2.22 days vs. 1.51± 3.97 days in the NIPPV group and the difference was statistically insignificant (p=0.478). Mean duration of CPAP/PEEP in the NCPAP group was 1.31± 0.53 days vs. 1.11 ± 0.70days of in the NIPPV group and the difference was statistically insignificant (p=0.146). Mean duration of oxygenation in the NCPAP group was 7.31± 5.82 days while it was 8.41± 6.70 in the NIPPV group and the difference was statistically insignificant (p=0.414) [Table 3]. Average length of stay in the NICU in NCPAP group was 13.96 ± 6.57days while as it was 10.85± 7.26 days in NIPPV group and the difference was statistically significant (OR=3.11, 95%CI=0.19-6.03, p=0.037).Mean duration of stay in the hospital in the NCPAP group was 18.39± 8.06 days while as it was 13.58± 7.53 days in NIPPV group and the difference was statistically significant (OR=4.8, 95%CI=1.49-8.12, p=0.004) [Table 3].

Table-3: Duration of mechanical ventilation, CPAP, oxygen, NICU and hospital stay in the two groups of patients

Variables	Mean ± Standard deviation		p-value
	CPAP (n=49)	NIPPV (n=40)	
Mechanical vent. duration (days)	1. 01 ± 2.22	1.51 ± 3.97	0.478
CPAP duration (days)	1.31 ± 0.53	1.11 ± 0.70	0.146
Oxygen duration (days)	7.31 ± 5.82	8.41 ± 6.70	0.414
NICU stay(days)	13.96 ± 6.57	10.85 ± 7.26	0.037
Hospital stay(days)	18.39 ± 8.06	13.58 ± 7.53	0.004
BPD: Bronchopulmonary dysplasia			

The mortality was 8.16% (4/49) patients in the NCPAP group and 2.50% (1/40) in the NIPPV group died and the difference was statistically insignificant (p=0.25). Around 14.2 % (7/49) patients in NCPAP group developed bronchopulmonary dysplasia vs. 2.5 % (1/40) in NIPPV group at 36 weeks of postmenstrual age and the difference was statistically significant (p=0.05, OR =0.15, 95%CI=0.01-1.30) [Table 2].

Discussion

It has been shown in previous studies that as a method of respiratory support NIPPV reduces the need for mechanical ventilation, duration of NICU and hospital stay. In this study the mean gestational age at admission in NCPAP and NIPPV group was statistically insignificant (p=0.648) which was similar to the study conducted by Kugelman et al [20] the mean gestation age was 30.6 ± 3.0 and 31.1 ± 2.3 in NCPAP and NIPPV group respectively (p=0.55). The mean birth weight in NCPAP and NIPPV group in the present study, was statistically insignificant (p=0.071) was similar to the study conducted by Kugelman et al [20] the mean birth weight was 1533 ± 603 and 1616 ± 494 respectively in NCPAP and NIPPV groups. In the present study males in NCPAP and NIPPV group was statistically insignificant (p=0.254) was similar to the study conducted by Kugelman et al [20] 60.97% were males in NCPAP group and 65.11% were males in NIPPV group and the difference was not statistically significant (p=0.82).

In this study neonates in NCPAP and NIPPV group born by cesarean was statistically insignificant (p=0.091) which was similar to the study conducted by Kugelman et al[20] 76% in NCPAP group and 69% in NIPPV group were born by cesarean section and the difference was statistically insignificant (p=0.81). In the present study the APGAR score at 5 min in NCPAP and NIPPV group, the difference was statistically insignificant (p=0.572). In the study by Kugelman et al

[20] the 5min APGAR score was 9 in both groups (p=0.11). In the study by Meneses et al [21], the 5 min APGAR score was 8 in both groups.

At 72 hour of life, patients in NCPAP and NIPPV groups were intubated and undergoing mechanical ventilation and the difference was statistically significant. In the study by Esmaeilnia et al [22] the need for mechanical ventilation at 72 hour of life was 17.6% in NCPAP group and 6% in NIPPV group and the difference was statistically significant (p=0.031) similar to our results. In the study by Oncel et al [23] the need for mechanical ventilation at 72 hour of life was 29% in NCPAP group and 13% in NIPPV group and the difference was statistically significant (p=0.005) similar to results of present study. This shows that the need for intubation and mechanical ventilation at 72 hour of life is significantly low in NIPPV than NCPAP group.

In the study by Kishore et al[24] 13.5% patients in NIPPV group and 35.9% patients in NCPAP group needed mechanical ventilation at 48 hour of life and the difference was statistically significant (p=0.024) similar to the present study results. Overall mechanical ventilation needed by patients in the NCPAP and NIPPV group was statistically significant (p=0.04). This suggests that the need for mechanical ventilation was decreased by >20% in NIPPV group compared to NCPAP group in the patients. In the study by Kishore et al [24] mechanical ventilation was needed by 18.9% in NIPPV group and 41% in NCPAP group (p=0.036). This suggests that NIPPV is associated with lower failure rate and failure rate decreased by 22.1% which was also statistically significant similar to our results.

In the study by Khalaf et al [25], mechanical ventilation was needed by 5.8% in NIPPV group and 40% in NCPAP group(p<0.01) suggesting lesser need for mechanical ventilation in the NIPPV group. The reason for failure was frequent apneas and desaturations in NCPAP group (14 patients) and increased PaCO2 (4 patients) and in the NIPPV group the reason for failure was requirement for increased Fi02 (3 patients) and apnea (4 patients) in this study. Similar results were reported by Tang et al [18], Kugelman et al [20] and Barrington et al [26]. In this study the mean duration of mechanical ventilation in NCPAP group and NIPPV group and was statistically insignificant (p=0.478). In the study by Kugelman et al[20] the mean duration of mechanical ventilation was 13.2 ± 15.8 days in NCPAP group and 10.2 ± 23.8 days in NIPPV group (p=0.67) the difference is statistically insignificant similar to our results.

In the study by Meneses et al [21] , the mean duration of mechanical ventilation was 5 days in NCPAP group and 7 days in NIPPV group and the difference was statistically insignificant(p=0.14), similar to the present results. In the NCPAP group 2 patients needed MV on day one , 2 on day two, 7 on day three, 2 on day 4,two on day 5, 2 on day 6 and 1 after day seven. In the NIPPV group 3 patients needed MV on day three and 2 on day 5. The time to mechanical ventilation was longer in NIPPV group compared to NCPAP group. Similar results were shown by Kishore et al [24] in their study.

The duration of respiratory support in NCPAP and NIPPV group was statistically insignificant (p=0.146). In the study by Kishore et al[24] mean duration of NCPAP was 1.83 days in NIPPV and 2.5 days in NCPAP (p=0.33), statistically insignificant similar to our results. In the study by Meneses et al[21], the mean duration of NCPAP was 9.6 ± 6.8 days in NIPPV and 9.4 ± 8.9 days in NCPAP group and the difference was statistically insignificant (p=0.65).

In the current study the mean duration of oxygen therapy was 7.31 ± 5.82 days in NCPAP group and 8.41 ± 6.70 days in NIPPV group and the difference was statistically insignificant (p=0.478). In the study by Kishore et al [24] the mean duration of O2 therapy was 3 days in both NCPAP and NIPPV groups (p=0.39), statistically insignificant, similar to our results. In the study by Meneses et al[21], the mean duration of oxygen was 20.4 ± 16 days in NCPAP group and 23.6 ± 22.6 days in NIPPV group and the difference was statistically insignificant(p=0.97).

Only 50% of patient in the NIPPV received surfactant replacement in the NIPPV group

(20/40) vs. 100% (49/49) in the NCPAP group (p=0.05), which was statistically significant. Repeat dose of surfactant was needed by 8.1% (4/49) in the NCPAP group vs. 5% (2/49) in NIPPV group (p=0.371) which was statistically insignificant. In the study conducted by Kishore et al[24], the need for repeat dose of surfactant was 7.7% in NCPAP group and 2.7% in NIPPV group (p=0.61) which was statistically insignificant similar to our results.

This study thus showed decreased need for surfactant therapy in NIPPV group as compared to NCPAP group. The duration of stay in the NICU was less in the NIPPV group than in the NCPAP group in the present study (P=0.037).Also the duration of hospital stay (P= 0.004) was significantly less in the NIPPV group than in the NCPAP. In the study conducted by Esmaeilnia et al[22], the duration of hospital stay was significantly less in NIPPV group compared to NCPAP group similar to our results (p=0.003). In the study by Bahman et al[27] the duration of hospital stay was significantly less (p<0.001) in NIPPV compared with NCPAP group similar to our results.

In this study neonatal mortality was 8.16% (4/49) in the NCPAP group vs. 2.50% (1/40) in the NCPAP group and the difference was statistically insignificant (p=0.072).In the study by Kishore et al[24], the neonatal mortality was 23% in NCPAP group and 13.5% in NIPPV group (p=0.44) similar to our results. In the study by Wood et al [28], the neonatal mortality was 3.3% in NCPAP and zero percent in NIPPV group and the difference was statistically insignificant (p=0.50) similar to our results. The incidence of BPD at 36 weeks post menstrual age was 14.2% (7/49) and 2.5% (1/40) in NCPAP and NIPPV groups respectively and the difference was statistically significant (P=0.05).

In the study by Kugelman et al[20], the incidence was 33% in NCPAP and 5% in NIPPV group which was statistically significant (p=0.03) similar to our results. This shows that NIPPV is associated with a significantly lower incidence of BPD than NCPAP. Also the combined incidence of BPD and death was 22.4% in the NCPAP group vs.5% in the NIPPV group which was statistically significant (P=0.02).

Conclusion

NIPPV not only decreases the need for mechanical ventilation in the first 72 of hours of life in preterm babies but also decreases the duration of NICU and hospital stay, decreases the need for surfactant replacement therapy, incidence of BPD and also the combined incidence of BPD and death in preterm babies in the study population.

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