Noninvasive Positive Pressure Ventilation or Conventional Mechanical Ventilation for Neonatal Continuous Positive Airway Pressure Failure

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ABSTRACT

Background: The aim of this study was to assess the success rate of nasal intermittent positive pressure ventilation (NIPPV) for treatment of continuous positive airway pressure (CPAP) failure and prevention of conventional ventilation (CV) in preterm neonates.

Methods: Since November 2012 to April 2013, a total number of 55 consecutive newborns with gestational ages of 26-35 weeks who had CPAP failure were randomly assigned to one of the two groups. The NIPPV group received NIPPV with the initial peak inspiratory pressure (PIP) of 16-20 cmH_2O and frequency of 40-60 breaths/min. The CV group received PIP of 12-20 cmH_2O and frequency of 40-60 breaths/min.

Results: About 74% of newborns who received NIPPV for management of CPAP failure responded to NIPPV and did not need intubation and mechanical ventilation. Newborns with lower postnatal age at entry to the study and lower 5 min Apgar score more likely had NIPPV failure. In addition, treatment failure was higher in newborns who needed more frequent doses of surfactant. Duration of oxygen therapy was 9.28 days in CV group and 7.77 days in NIPPV group ($P = 0.050$). Length of hospital stay in CV group and NIPPV groups were 48.7 and 41.7 days, respectively ($P = 0.097$).

Conclusions: NIPPV could decrease the need for intubation and mechanical ventilation in preterm infants with CPAP failure.

Keywords: Conventional ventilation, continuous positive airway pressure failure, nasal intermittent positive ventilation, premature infant

Original Article

INTRODUCTION

Before the invention of mechanical ventilation, premature infants who developed respiratory distress syndrome (RDS) either died in the 1st week after birth or survived without respiratory morbidity.[1] The survival of premature infants improved significantly with the introduction of mechanical ventilation. However, intubation and mechanical ventilation

have been associated with acute complications including air leak syndromes, subglottic stenosis, bradycardia due to stimulation of vagus nerve and infection. Moreover, chronic complications such as bronchopulmonary dysplasia (BPD) and retinopathy of prematurity may occur following mechanical ventilation.[2,3] In an effort to decrease ventilator-induced lung injury, alternative techniques of invasive ventilation have been employed.[4]

General implications of ventilator-induced lung injuries are: Volu/barotraumas, injury related to lung over distention or stretching of pulmonary structures, atelectrauma injury caused by alveolar collapse and biotrauma, injury caused by hyperactive inflammatory responses secondary to bacterial airway colonization.[5,6] Because of many complications of mechanical ventilation, gentler modes of ventilation including nasal continuous positive airway pressure (NCPAP) are now the primary mode of respiratory support in preterm infants.[7] CPAP can improve oxygenation by increasing functional residual capacity and decrease work of breathing by reducing airway resistance.[1] Therefore, it is useful for treatment of RDS at the earliest signs of respiratory distress, postextubation respiratory support, and stabilization of newborns with labored respiration or cyanosis in the delivery room.[8,9] In addition, CPAP splints the upper airways during respiration and prevents collapse of the pharynx during expiration thereby it is effective for management of recurrent apnea in newborn infants.[10,11]

However, the rate of CPAP failure is relatively high and diminishing the time newborns spend in mechanical ventilation is required by using alternative methods instead of mechanical ventilation for management of CPAP failure.[12] Nasal intermittent positive pressure ventilation (NIPPV) is a form of noninvasive respiratory support that combines NCPAP with intermittent ventilator breaths and offers more ventilator support than NCPAP.[4] Some researchers recommended the use of synchronized NIPPV for respiratory support after extubation.[9] Others proposed NIPPV for initial management of RDS or treatment of apnea of prematurity.[4,10] The primary advantage of NIPPV is maintaining higher mean airway pressure than CPAP. This provides higher capability to recruit collapsed alveoli, sustain end expiratory lung volume, decrease respiratory dead space, improve lung mechanics, and accommodate oxygenation. In addition, NIPPV increases tidal volume and provides sigh breaths, which can increase gas exchange and decreases airway collapse.[12,13]

The purpose of this study was to assess the success rate of NIPPV as a noninvasive method for management of CPAP failure and prevention of intubation and mechanical ventilation in premature infants.

METHODS

Patient and setting

This was a prospective clinical trial comparing the efficiency of NIPPV and mechanical ventilation for management of CPAP failure in premature infants. During a period of 5 months since November 2012 to April 2013, a total number of 55 consecutive newborns delivered in Alzahra and Shahid Beheshti University Hospitals were enrolled into the study.

Premature infants with gestational ages (GAs) of 26-35 weeks who had CPAP failure were enrolled to the study. CPAP failure was defined as: The need for FiO_2 more than 60% and maximum CPAP of 8 cmH_2O for maintaining SpO_2 of 88-95% and/or pH <7.2 and PCO_2 more than 60 and/or more than three episodes of apnea with bradycardia (heart rate <80/min).

Exclusion criteria were: The need for intubation and mechanical ventilation before allocation, nasopharyngeal pathology; coanal atresia; cleft/lip palate; major congenital anomalies especially thoracic or cardiac anomalies; intra-ventricular hemorrhage (IVH) Grade 3 or 4 on admission, and parental refusal to participate in the research project. Ethic approval was obtained from Isfahan University of Medical Sciences Ethics Committee and informed written parental consent was obtained before participation.

Procedure

The allocation sequence was included computer-generated random numbers in a blocked design. Infants were randomized to receive either NIPPV or conventional ventilation (CV), from concealed envelopes opened by nonstudy personnel.

Demographic data including birth weight, GA, Apgar score at 5 min, antenatal steroid use and postnatal age at the time of the entrance to the study, were recorded by one of the investigators. We also assessed the incidence of complications such as pneumothorax, IVH, BPD, necrotizing enterocolitis (NEC), and patent ductus arteriosus (PDA) in the two groups. In addition, the underlying diseases that led to CPAP failure such as RDS, apnea of prematurity and apnea due to other causes were recorded. Cranial ultrasonography for evaluation of IVH was performed on the 3rd and 7th days after birth. Duration of oxygen therapy, length of hospital stay, and duration of respiratory support were recorded.

Variables and assessments

We used a time cycled, pressure limited neonatal ventilator (bear Cub 750 psv) for newborns allocated to the study. The initial setting for NIPPV were peak inspiratory pressure (PIP) of 16-20 cmH_2O, positive end expiratory pressure (PEEP) of 4-6 cmH_2O, inspiratory time (TI) of 0.4-0.5 s and frequency of 40-60 breaths/min and a flow of 8 L/min. The initial setting for CV group was PIP of 12-20 cmH_2O (according to patient's need), PEEP of 4-6 cmH_2O, TI of 0.35-0.4 s and frequency of 40-60 breaths/min and a flow of 8 L/min. Ventilator setting were adjusted so that the target range of SPO_2 (88-95%) was obtained. In both groups, we have taken blood samples for arterial blood gas 1 h after initiation of treatment protocol and then every 6 h or 1 h after each changes in ventilator parameter. Sterile nasal prongs (Argyle, Sherwood Medical Co, St. Louis, MO, USA) were used to provide NIPPV. We selected the proper size of the prongs based on infants' weight as follows: Large for infants weighing >1500 g, small for infants 1000-1500 g and x small for infants <1000 g. We did not use a pacifier or chin strap to decrease the risk of air leak syndrome.

The infants in the NIPPV group were intubated if they needed a PIP of >25 cmH_2O and/or frequency of >60 breaths/min, and then the patient was treated with CV.

Definitions

Gestational age was determined by maternal menstrual history. Pregnancy-induced hypertension was specified by a systolic blood pressure of >140 mmHg and a diastolic blood pressure of >90 mmHg in the presence of proteinuria (>300 mg/day) and non-dependent edema. RDS was defined as the presence of respiratory distress and a characteristic chest radiograph. PDA was established by echocardiography. IVH was confirmed by cranial ultrasonography based on Papile's classification.[14] BPD was documented by the need for supplementary oxygen at 36 weeks of corrected GA and characteristic radiographic changes.[15] Sepsis was diagnosed by a positive blood culture. NEC was diagnosed on the basis of Bell's criteria.[16] Apgar score was calculated by one of the researchers using five parameters including heart rate, respiratory effort, muscle tone, reflex irritability and color.[17] We were treated RDS based on our standard protocols. We were used surfactant as rescue therapy in newborns who needed intubation and mechanical ventilation or if they were on noninvasive modes with FiO_2 >40%. Newborns were weaned form NIPPV or CV to NCPAP based on our standards practice.

The primary outcome was to determine the success rate of NIPPV for prevention of mechanical ventilation. Secondary outcomes were duration of ventilation and oxygen therapy in two groups.

Statistical analysis

The primary target sample size for this pilot study was a total of 50 patients. However, we entered 28 infants in the control group and 27 infants in the intervention group.

Data analysis was performed using SPSS software (version 21, SPSS Inc, Chicago, IL) and comparison were made using independent Sample T-test, Mann-Whitney, Chi-square test, and Fischer exact test as appropriate and $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 55 newborns were enrolled in the study. The study flow is shown in Figure 1. The maternal and infant characteristics are shown in Table 1. There were no significant differences between two groups with regard to birth weight, GA, and gender. The maximum and minimum of birth weights were 700 and 2150 g in CV group and 800 and 1850 g in NIPPV group. GA ranged from 26 to 34 weeks in CV group and 27 to 35 weeks in NIPPV group. Postnatal age at entry to the study was significantly lower in the CV group. We did not find significant differences between groups

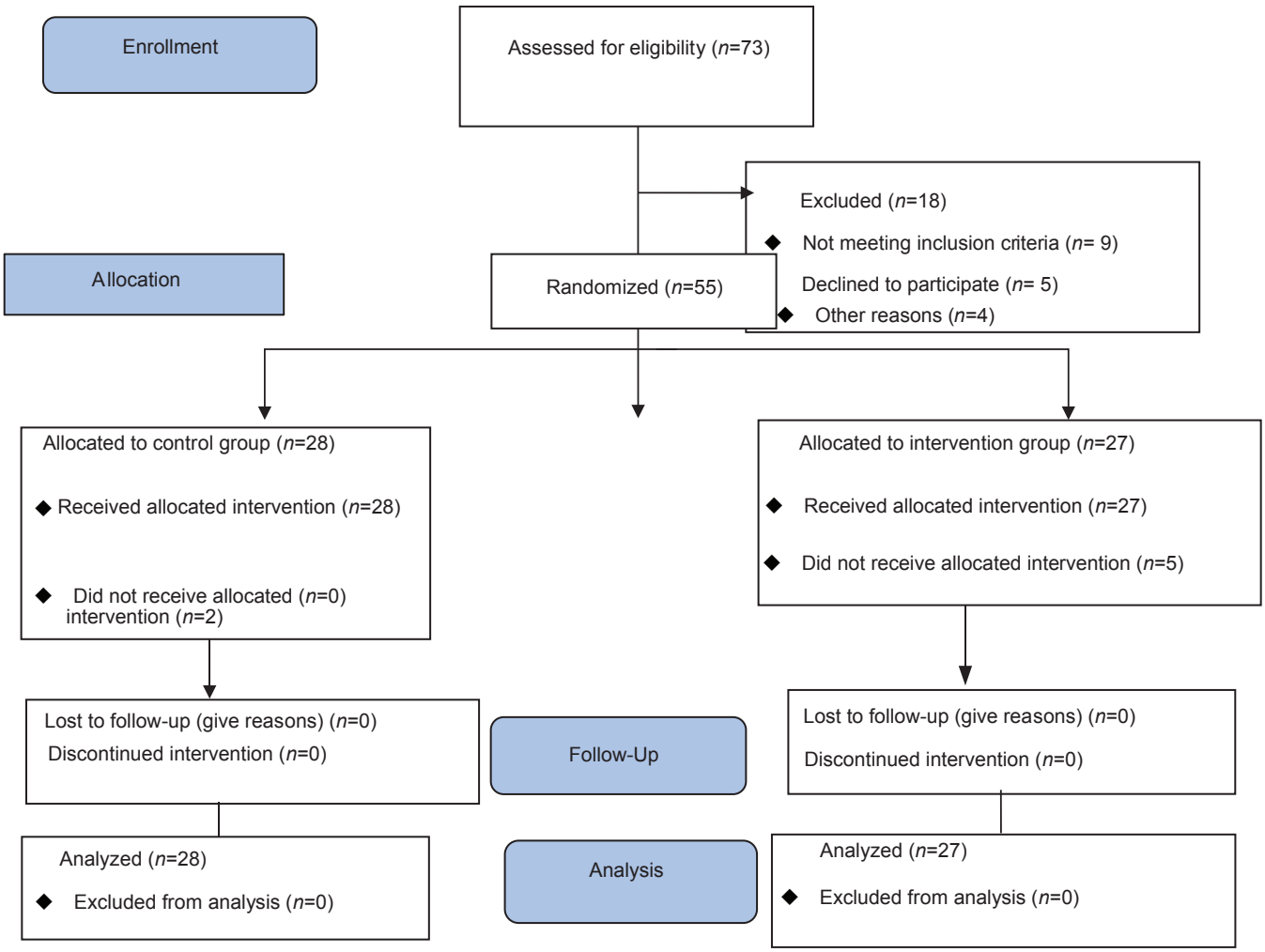

Figure 1: The study flow

with regards to the incidence of RDS, PDA, IVH, NEC, and sepsis [Table 2].

Although fewer infants in the NIPPV group experienced pneumothorax compared to CV group (6 instead of 2) this difference was not statistically significant. Furthermore, fewer infants in the NIPPV group compared to CV group were oxygen dependent at 28 days, but this difference was not significant.

There were no differences in the blood gasses (PH, PCO_2, PO_2, and HCO_3) at 1, 6, 12, 18 and 24 h postintubation or after treatment with NIPPV in the two groups.

Duration of oxygen therapy was 9.28 days in CV group and 7.77 days in NIPPV group (P = 0.050). Length of hospital stay in CV group and NIPPV groups were 48.7 and 41.7 days respectively (P = 0.097). There were no differences in the other common neonatal morbidities between the two groups.

About 74% of newborns who received NIPPV for management of CPAP failure responded to NIPPV and did not need intubation and mechanical ventilation. However, seven infants (25.9%) receiving NIPPV did not respond to NIPPV and needed intubation and mechanical ventilation. To find factors that may increase treatment failure with NIPPV we performed intergroup comparisons [Table 3]. Newborns with lower postnatal age at entry to study and lower 5 min Apgar score more likely had NIPPV failure. In addition, treatment failure was higher in newborns who needed more frequent doses of surfactant.

DISCUSSION

Because of possible complications of endotracheal intubation and mechanical ventilation

Table 1: Demographic and clinical characteristics of newborns in two groups

	CV group (*n*=28)	NIPPV group (*n*=27)	*P* value
Postnatal age at entry (days)			
Median (minimum, maximum)	1.0 (3, 0.08)	2.0 (7, 0.08)	0.03
Birth weight (g)±(SD)	1260 (340)	1159 (227)	0.2
Gestational age (weeks) (SD)	29.64 (2.6)	28.72 (2.4)	0.18
Gender (male number)	14	13	0.553
Apgar at 5 min (mean±SD)	7.3 (1.4)	7.6 (1.1)	0.56
Number of surfactant applications >1			
Surfactant dose use	10	13	0.53
Number of Ibuprofen course use >1	3	5	0.21
Maternal PIH (*n*) (%)	6 (21)	8 (29)	0.349
Antenatal steroids (*n*) (%)	22 (78)	23 (85)	0.389
Sepsis (*n*) (%)	9 (32)	10 (37)	0.461

CV=Conventional ventilation, NIPPV=Noninvasive positive pressure ventilation, SD=Standard deviation, PIH=Pregnancy-induced hypertension

including laryngeal and tracheal injury, increased incidence and severity of BPD and increased hospital acquired sepsis and pneumonia, using noninvasive modes of respiratory care could have many advantages for preterm infants. Our study reveals that NIPPV is a good alternative mode to mechanical ventilation for management of CPAP failure. However, about 26% of newborns who underwent NIPPV for treatment of respiratory failure did not respond to this mode of noninvasive ventilation and needed intubation and mechanical ventilation. We found that newborns with lower postnatal age at entry to the study and lower 5 min Apgar score more likely had NIPPV failure. In addition, the failure rate of NIPPV was higher in newborns who needed more frequent doses of surfactant.

The higher rate of NIPPV failure in newborns with lower 5 min Apgar score is probably due to decreased central respiratory drive following birth hypoxia. Likewise, the higher rate of NIPPV failure in newborns who needed more frequent doses of surfactant may be due to more severe lung disease and lower pulmonary compliance in these newborns leading to more severe respiratory failure.

There are a few studies comparing NIPPV and CV for management of respiratory disorders in premature infants. Lampland *et al*. conducted a study to compare the effects of NIPPV and synchronized intermittent mandatory ventilation (SIMV) on markers of physiologic tolerance and lung injury in spontaneously breathing piglets with RDS. They found that interstitial inflammation was significantly higher in SIMV group.[18]

Another study was done by Bhandari *et al*. on preterm infants with birth weights of 600-1250 g to compare the outcomes of infants with RDS, postsurfactant, extubated to SNIPPV or continued on CV. They demonstrated that use of SNIPPV as the primary mode of ventilation could decrease the need for mechanical ventilation. In addition, more infants in the CV group had BPD and death, compared to SNIPPV group. Nevertheless, there were no significant differences between two groups in the incidence of other morbidities such as pneumothorax, IVH, and NEC.[4]

We also showed that the total duration of oxygen therapy and total duration of respiratory support did not significantly differ between groups. However, the total duration of oxygen therapy and total duration of ventilator support in our study were shorter than Bhandari's study. We speculated that this difference may be due to lower birth weight and GA of newborns of the Bhandari's study.

Kishore *et al*. conducted a study to find the failure rate of NIPPV and NCPAP as the primary mode of respiratory support for preterm infants with RDS. They demonstrated that the failure rate (defined as the need for intubation and mechanical ventilation) at 48 h and 7 days was significantly less among infants randomized to NIPPV compared to NCPAP (13.5% vs. 39.5%).[19] We supposed that the higher rate of NIPPV failure in our study is due to the fact that we used NIPPV for infants with CPAP failure and not as the primary mode for management of RDS.

The beneficial effects of NIPPV could be justified by an explanation of Kiciman *et al*. They had shown that thoracoabdominal motion asynchrony could decrease using nasal SIMV compared to endotracheal CPAP and NCPAP and speculated that this effect may be owing to removal

Table 2: NICU outcomes

	CV group (*n*=28)	NIPPV group (*n*=27)	*P* value
NCPAP days (mean±SD)	1.93 (2.2)	2.9 (3.2)	0.16
BPD (%)	9 (32.1)	5 (18.5)	0.198
Deaths (%)	4 (14)	2 (7.4)	0.352
PDA (Ibuprofen use) (%)	8 (28)	9 (33)	0.464
IVH (*n*) (%)	11 (39)	7 (25)	0.222
NEC (*n*) (%)	5 (17)	6 (22)	0.473
Pneumothorax (*n*) (%)	6 (21)	2 (7)	0.137
Length of hospital stay (days) (mean±SD)	48.7 (14)	41.7 (12.8)	0.097
Total duration of O_2 supplemental			
Median (minimum, maximum)	26 (12,58)	26 (3,52)	0.27
Ventilation days (±SD)			
Median (minimum, maximum)	9 (2, 14)	9 (3, 26)	0.57
RDS (surfactant use %) (%)	22 (78)	22 (81)	0.527
Apnea of prematurity (*n*) (%)	10 (35)	12 (44)	0.350
Apnea for other reasons (*n*) (%)	3 (10)	3 (11)	0.648
Arterial blood gas: Mean±SD			
PH-1 h	7.25 (0.09)	7.30 (0.09)	0.08
PCO_2-1 h	51.2 (16.8)	40.5 (13.64)	0.12
HCO_3-1 h	19.7 (3.35)	17.95 (3.86)	0.08
PH-6 h	7.27 (0.1)	7.30 (0.09)	0.28
PCO_2-6 h	47.42 (16.03)	41.2 (12.02)	0.11
HCO_3-6 h	19.03 (4.01)	18.2 (3.7)	0.43
PH-12 h	7.31 (0.067)	7.30 (0.09)	0.52
PCO_2-12 h	47.5 (18.33)	40.5 (7.4)	0.06
HCO_3-12 h	18.74 (4.05)	18.11 (3.58)	0.54
PH-18 h	7.32 (0.08)	7.30 (0.1)	0.34
PCO_2-18 h	41.55 (7.75)	42.36 (12.66)	0.77
HCO_3-18 h	19.37 (2.6)	18.5 (2.96)	0.26
PH-24 h	7.33 (0.08)	7.30 (0.08)	0.16
PCO_2-24 h	43.40 (8.2)	44.29 (11.6)	0.74
HCO_3-24 h	20.01 (2.06)	20.26 (4.08)	0.78

NICU=Neonatal intensive care unit, CV=Conventional ventilation, NIPPV=Noninvasive positive pressure ventilation, NCPAP=Nasal continuous positive airway pressure, BPD=Bronchopulmonary dysplasia, SD=Standard deviation, PDA=Patent ductus arteriosus, IVH=Intra-ventricular hemorrhage, NEC=Necrotizing enterocolitis, RDS=Respiratory distress syndrome

of endotracheal tube resistance or impressive stabilization of the chest wall. Finally, they concluded that nasal SIMV could be an effective mode of respiratory support for premature newborns who need minimal respiratory support.[20]

There are several categories of studies using NIPPV for respiratory support of premature infants. The first category of studies was compared NIPPV and NCPAP for management of RDS immediately after INSURE technique. Gizzi *et al*. carried out a study to compare synchronized NIPPV and NCPAP used after INSURE technique in preterm newborns with RDS and demonstrated that NIPPV immediately after INSURE procedure could significantly decrease the need for mechanical ventilation.[21] Similarly, Kugelman *et al*. demonstrated that NIMV compared with NCPAP could decrease the need for intubation and mechanical ventilation.[22] Likewise, Ramanathan *et al*. conducted a study on 110 preterm neonates <30 weeks GA who needed surfactant therapy during first 60 min after birth for RDS and showed that NIPPV compared to NCPAP could reduce the need for intubation and mechanical ventilation and the incidence of BPD in premature infants.[23]

Recently, Kirpalani *et al*. conducted a study to compare the effects of NIPPV and NCPAP as the first respiratory support during the first 28 days of life and found that 33.9% of newborns in the NIPPV group and 31% of newborns in the NCPAP group experienced BPD. The frequency of air leak syndromes, NEC and duration of respiratory support were not significantly different between groups.[24] We also found no significant difference in the rates of BPD and other neonatal morbidities between groups.

The second category of studies was assessed the effectiveness of NIPPV for prevention of respiratory failure after extubation.

Friedlich, *et al*. compared the incidence of respiratory failure after extubation in preterm newborns randomized to take either NCPAP or nasopharyngeal synchronized intermittent mandatory ventilation (NP-SIMV) and found that postextubation respiratory failure was significantly lower in the NP-SIMV group.[25]

Recently, Kahramaner *et al*. have reported that using unsynchronized NIPPV is better than NCPAP for prevention of extubation failure in preterm newborns.[26]

The third category of studies evaluated the effects of NIPPV for treatment of apnea in preterm infants. Ryan *et al*. compared the effects of NCPAP and aminophylline versus NIPPV alone for management of idiopathic apnea in preterm infants and concluded that NIPPV had no advantage over NCPAP.[27] Lin *et al*. showed that NIPPV is more efficient than NCPAP for prevention of recurrent apnea in premature infants.[28]

However, the length of hospital stay and duration of ventilation therapy did not differ significantly between groups.

Although there are few studies evaluated success rate of NIPPV as an initial mode of RDS management and for treatment of apnea of prematurity, to the best of our knowledge, this is the first study that assessed the success rate of NIPPV for treatment of CPAP failure as an alternative to mechanical ventilation.

Our study had some limitations. First of all, we did not categorize newborns on the basis of severity of respiratory problem and Apgar score. Therefore, we had relatively high rate of NIPPV failure. If we were excluded infants with very severe RDS and very low Apgar score the failure rate may be decreased.

Table 3: Comparison of newborn characteristics based on response to NIPPV

	NIPPV without intubation (*n*=20)	Intubate after NIPPV (*n*=7)	*P*
Postnatal age at entry (days)			
Median (minimum, maximum)	2 (0.25, 7)	1 (0.8, 1)	0.09
Birth weight (g)±(SD)	1140 (294)	1078±498	0.7
Gestational age (weeks)±(SD)	29.08 (2.4)	29.28±2.3	0.86
Gender			
Male/female	7/11	4/3	0.6
Apgar at 5 min±(SD)	8 (1.4)	6.7 (1.1)	0.04
Surfactant dose use	1.6	1.5	0.01
Ibuprofen course	1.6	1.5	0.09
Maternal PIH *n* (%)	6 (33.3)	0 (0)	0.08
Antenatal steroids *n* (%)	15 (83.3)	4 (57.1)	0.29
Sepsis s*n* (%)	6 (33.3)	2 (28.5)	1

SD=Standard deviation, NIPPV=Noninvasive positive pressure ventilation, PIH=Pregnancy-induced hypertension

Secondly, we did not assess short term complications of intubation such as the severity of pain, bradycardia, laryngeal trauma and long-term complications such as hoarseness and subglottic stenosis in newborns who required mechanical ventilation. In addition, this study is a pilot study with small sample size. Therefore, the lack of significant differences in the rate of complications between two groups may be due to this constraint. In addition, the results should be interpreted adequately.

CONCLUSIONS

It appears that NIPPV is a good alternative to invasive mechanical ventilation in premature newborns with respiratory failure. Anyway some infants did not respond to this mode of respiratory support and require mechanical ventilation specially newborns with lower postnatal age at entry to study, lower 5 min Apgar score and newborns who need more frequent doses of surfactant.

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