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A Comparison of the Effect of Nasal bi-level Positive Airway Pressure and Sigh-positive Airway Pressure on the Treatment of the Preterm Newborns Weighing Less than 1500 g Affiliated with Respiratory Distress Syndrome

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ABSTRACT

Background: Nowadays, administering noninvasive positive airway pressure (PAP) is considered as the building block for the management of respiratory distress syndrome (RDS). Since nasal continuous PAP (n-CPAP) established its roots as an interventional approach to treat RDS, there have always been concerns related to the increased work of breathing in newborns treated with this intervention. Therefore, respiratory support systems such as nasal bi-level PAP (N-BiPAP) and sigh-PAP (SiPAP) have been developed during the last decade. In this study, two respiratory support systems which, unlike n-CPAP, are categorized as cycled noninvasive ventilation, are studied.

Methods: This study was a randomized clinical trial done on 74 newborns weighing 1500 g or less affiliated with RDS hospitalized in NICU at Al-Zahra Hospital from October 2012 to March 2014. Patients were randomly assigned to two respiratory support groups of N-BiPAP and SiPAP. Each group contained 37 newborns who were compared, according to their demographic characteristics, duration of noninvasive ventilation, the need to administer surfactant, apnea incidence, the need for mechanical ventilation, pneumothorax, intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), the duration of oxygen supplement administration, and chronic lung disease (CLD).

Results: The average duration of noninvasive respiratory support, and the average duration of the need for oxygen supplement had no significant difference between the groups. Moreover, apnea incidence, the need for mechanical ventilation, pneumothorax, IVH, PDA, CLD, the need for the second dose of surfactant, and the death rate showed no significant difference in two groups.

Conclusions: In this study, SiPAP showed no significant clinical preference over N-BiPAP in the treatment of the newborns with RDS weighing <1500 g.

Keywords: Nasal bi-level positive airway pressure, premature newborn, respiratory distress syndrome, sigh-positive airway pressure

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INTRODUCTION

Prematurity is still considered a health issue in the United States. In 2008, 12.3% of live birth had the

gestational age of <37 weeks.[1] Prematurity caused 6.27 deaths in each 1000 live births in the United States in 2007.[2] In 2003, diseases related to prematurity were considered as responsible for 17% of all newborn deaths; it is estimated that half of these deaths (49%) happened among newborns weighing <1000 g. Respiratory distress syndrome (RDS) and broncho-pulmonary dysplasia (BPD) are categorized as the most prevalent challenges leading to death in this group. Despite the increasing application of corticoid-steroids before birth and surfactant replacement aiming at managing the RDS, BPD prevalence in very low birth weight (VLBW) newborns showed no significant change. According to BPD pathogenesis, although genetic issues are concerning half of the patients, other various factors such as chorioamnionitis, hyperoxia stress, pulmonary edema, nosocomial infections, and injuries induced by respiratory management are considered as influential factors.[3]

It was Gregory *et al.* (1971) who emphasized and implicated CPAP as an intervention for the newborns with RDS. Similarly, subsequent studies revealed that CPAP can effectively assist RDS management with mechanisms such as functional residual capacity (FRC) increase accompanied by PaO_2 level improvement, pulmonary compliance improvement, better establishment of respiratory airways, diaphragm function reinforcement, alveolar collapse prevention, and decrease of gradient oxygen pressure in the level of alveolar arterial gradient oxygen.[4]

At the moment, administering nasal continuous PAP (nCPAP) and surfactant administration are considered as the ground stones and the first level of clinical intervention in treatment of the newborns affiliated with RDS, especially in extremely low birth weight newborns; however, this intervention necessitates INSURE method (Intubation Surfactant Extubation) for surfactant administration.[5-8]

Although nCPAP is regarded as the standard care for respiratory management in newborns affiliated with RDS, there are quite a few concerns about the side effects and the shortcomings of this system in treatment of the newborns such as an increase in development of air leak syndrome, lung over distension, decrease in compliance which results in increased work of breathing (WOB), excessive increase in intrathoracic pressure followed by a decrease in venous return, which leads to a decrease in cardiac output.[9]

In order to minimize the side effects of nCPAP, which is considered as a noncycled respiratory support in noninvasive ventilation, noninvasive cycled respiratory support systems have been developed during the last decade, which aim at noninvasive respiratory support with the minimum complications.[10]

According to terminology, as the technological characteristics of cycled noninvasive respiratory support systems differ based on their functioning basics, they include a range of interventions including:

- Nasal intermittent positive pressure ventilation (NIPPV)
- Synchronized nasal intermittent positive pressure ventilation (SNIPPV)
- Nasal synchronized intermittent ventilation
- Nasal bi-level positive airway pressure (N-BiPAP)
- Noninvasive pressure support ventilation (NI-PSV)
- Sigh-PAP (SiPAP).

In N-BiPAP and SiPAP noninvasive respiratory supports, the injector is definitely of IFD type, and the system produces two levels of PAP with flow control. The inspiratory PAP, which is referred to as IPAP, as opposed to the expiratory PAP (EPAP), which is called EPAP, can recruit alveoli, improve establishment of FRC, prevent possible alveolar atelectasis, and eventually decrease the WOB with sigh mechanism, which gives the system potential advantages over noncycled-noninvasive ventilation (cycled-NIV). In SiPAP, the pressure level change from EPAP to IPAP is controlled by a capsule trigger (Graseby capsule) placed over the abdomen; whereas in N-BiPAP, the pressure level change is based on the time-cycled system.[11]

Considering the potential capabilities of N-BiPAP and SiPAP in administering noninvasive respiratory support in treatment of newborns RDS as compared to noncycled-NIV, we decided to include the comparison of SiPAP and N-BiPAP in the framework of a clinical trial.

METHODS

Study design and participants

This study is a prospective randomized clinical trial done on VLBW newborns affiliated with RDS, hospitalized at the NICU division of Al-Zahra Hospital, an affiliation of Isfahan Medical University, from September 2011 to January 2013.

Inclusion criteria included newborns with <1500 g birth weight with clinical signs of RDS (tachypnea, intercostal retraction, nasal flaring, granting, and the need for inspiratory oxygen fraction more than 21%). The exclusion criteria included congenital abnormality at birth and perinatal asphyxia (Apgar score of 0–3 at min 5, umbilical cord pH <7, and umbilical cord bicarbonate <12 mEq/L).[9]

Of 90 newborns that were born weighing <1500 g in Al-Zahra Hospital, 16 newborns were excluded due to parental discontent or not meeting inclusion criteria [Figure 1]. The 74 newborns that were eligible to enter the study were treated by N-BiPAP and SiPAP after written commitment was attained from their parents. In order to randomize the trial, the newborns with even document numbers were placed in SiPAP group and the newborns with odd document numbers were placed in N-BiPAP group. All the assigned newborns were followed up. Unfortunately, the death of the newborns caused discontinuation of follow for 6 newborns in N-BiPAP group, and 4 newborns in Si-PAP group [Figure 1].

Procedures and variables assessment

For the newborns in N-BiPAP group, at first IFD injector (Viasys Healthcare Inc., Cardinal Health, Dublin, Ohio, U.S.) was administered by proper nasal prongs; then, using Fabian nCPAP noninvasive respiratory support system (Acutronic Medical System AG, Switzerland), at first the positive pressure of equal to 4 cmH_2O was defined as EPAP and pressure equal to EPAP + 3 cmH_2O for the duration of a second was considered as IPAP. The pressure exchange rate for the newborn was set to 20 times/min.[12]

In case, the newborn needed inspiratory oxygen fraction of higher than 40% to maintain oxygen saturation in the right hand at 90–95%, the newborn would receive 100 mg/kg of survanta per INSURE method.[13]

In case, the newborn's need for the inspiratory oxygen fraction of higher than 40% was consistent to maintain the oxygen saturation level in an acceptable range, after 6 h from the last administration of surfactant, survanta would be administered again, and as necessary, the full course of treatment (maximum 4 days) would be observed. Newborns were monitored for their capillary blood gas (CBG) before and after surfactant administration, and also every 12 h after that, and due to the results, appropriate interventions were undertaken in managing the mechanical ventilation. If oxygen saturation in the right hand were not in the acceptable range despite the administration of the surfactant, first EPAP would be increased 1–2 cmH_2O and then FiO_2 would also be increased 5–10%, if necessary.[14]

During weaning, first EPAP would be decreased and then FiO_2 would be reduced and at EPAP = 4 cmH_2O, and FiO_2 ≤25%, the newborn would be detached from respiratory support. During respiratory support, the focus was on adjusting the relation between EPAP and FiO_2 according to the following Table 1.[12]

Incidence of any of the following indications led to discontinuation of noninvasive respiratory support and the start of intubation and invasive respiratory support:

- Inability to maintain acceptable ventilation and respiratory failure (pH <7.2 and PCO_2 >65 mmHg).[14]

Table 1: Respiratory management under BiPAP

FiO_2	IPAP (cmH_2O)	EPAP (cmH_2O)
<0.3	8	5
0.3-0.5	9	6
>0.5	10	7

BiPAP=Bi-level positive airway pressure, IPAP=Inspiratory positive airway pressure, EPAP=Expiratory positive airway pressure

- More than three times apnea incidence within 1-h, which necessitated stimulation or bag and mask ventilation.[15]
- The need for FiO_2 >75% in order to maintain oxygen saturation in the range of 90–95%.[16]

For the newborns in SiPAP group, IFD injector (Viasys Healthcare) was placed by appropriate prongs and using SiPAP (Viasys Healthcare) support system, they were treated with this intervention. Graseby capsule was placed between the umbilicus and the xiphoid process and respiratory management indications in this group were the same as N-BiPAP group. However, pressure exchange rate is not defined for this system, and the operator must define the pressure levels according to the flow velocity in the system.[17]

In the first 72 h after birth, echocardiography was done over the newborns to define if the ductus arteriosus was open. The newborns were monitored on the 3rd, 7th, and 14th day after birth for intraventricular hemorrhage (IVH) through brain sonographer. On the answer sheet, demographic characteristics, the length of the noninvasive respiratory support, administered surfactant doses, apnea incidence, the need for mechanical ventilation, the length of oxygen supplement (if the newborn continued to need oxygen supplement for more than 28 days after birth, chronic lung disease would be diagnosed), and pneumothorax were recorded.

Statistical analysis

IBM Statistical Package of Social Sciences, version 18, was used to administer *t*-tests, Pearson correlation coefficient, and Chi-squared test. The detailed results of the analysis will be given in the results section.

RESULTS

Demographic characteristics of the two groups are shown in Table 2. In N-BiPAP group, 30 newborns (81%) were delivered through cesarean and 7 newborns were delivered vaginal; in SiPAP group 35 newborns (94.6%) were delivered through cesarean and 2 newborns (5.4%) were delivered vaginal. No significant difference was observed between the two groups ($P = 0.15$).

The average gestational age in N-BiPAP group was 29.59 ± 2.5 weeks, whereas the same average for SiPAP group was 29.48 ± 2.4 which showed no significant difference ($P = 0.852$). The average weight was

1131 ± 272 g in N-BiPAP and 1160 ± 239 g in SiPAP, which showed no significant difference (P = 0.623). The average minutes 5 Apgar score was 7.7 ± 1 in N-BiPAP group and 8.1 ± 0.7 in SiPAP, which was not significantly different (P = 0.06). Among 83% of mothers in N-BiPAP group had received steroid before the end of pregnancy as compared to 70.3% of the mothers in SiPAP group; the difference was not statistically significant (P = 0.26). Premature rupture of membrane for 18 h or more happened for 6 cases (16.2%) in N-BiPAP group and 9 cases (24%) in SiPAP group, which does not show any significant difference (P = 0.56).

In Table 3, both group's outcome incidence frequencies are compared. The comparison of the duration of noninvasive treatment in both groups showed no statistically significant difference (P = 0.22). The duration of oxygen administration was not significantly different in the two groups (P = 0.07). The incidence of the need for surfactant administration showed no significant difference in the groups (P = 0.81). The incidence of open ductus arteriosus was not significantly different in the groups (P = 0.8). The apnea incidence comparison showed no significant difference (P = 0.80). The need for invasive ventilation showed no significant difference (P = 1). The incidence of IVH showed no significant difference (P = 0.48). The incidence of pneumothorax, chronic respiratory disease, and death was not significantly different in the groups.

Table 2: Demographic characteristics of newborns in two groups

	N-BiPAP	SiPAP	*P*
Gestational age (week) (mean±SD)	29.59±2.5	29.48±2.4	0.85
Sex (*n*) (%)			
Male	18 (48.6)	20 (54.1)	0.81
Female	19 (51.4)	17 (45.9)	
Weight (g) (mean±SD)	1131±272	1160±239	0.623
Apgar (mean±SD)			
1	5.6±1.5	6.2±1.3	0.11
5	7.7±1	8.1±0.7	0.06
ROM ≥18 h (*n*) (%)	6 (16.2)	9 (24.3)	0.56
Steroid administration to mother (*n*) (%)	31 (83)	26 (70.3)	0.26
Delivery (*n*) (%)			
C/S	30 (81.1)	35 (94.6)	0.15
NVD	7 (18.9)	2 (5.4)	

SD=Standard deviation, N-BiPAP=Nasal bi-level positive airway pressure, SiPAP=Sigh-positive airway pressure, C/S=Cesarean section, NVD=Normal vaginal delivery, ROM=Rupture of membranes

Table 3: Respiratory and clinical outcomes in two groups

	BiPAP	SiPAP	*P*
Length of noninvasive support (h) (mean±SD)	37.08±11.12	42.49±24.12	0.22
Length of O_2 administration (h) (mean±SD)	75.30±28.02	92.19±47.60	0.07
Apnea (*n*) (%)	10 (45.5)	12 (54.5)	0.80
IMV (*n*) (%)	5 (50.0)	5 (50.0)	1.00
IVH (*n*) (%)	6 (66.7)	3 (33.3)	0.48
Grade I	2 (66.7)	1 (33.3)	
Grade II	4 (66.7)	2 (33.3)	
Grade III	0 (0.0)	0 (0.0)	
Grade IV	0 (0.0)	0 (0.0)	
Pneumothorax (*n*) (%)	1 (100)	0 (0.0)	1.00
Surfactant (*n*) (%)	16 (53.3)	14 (46.7)	0.81
Totally two dose	7 (38.9)	11 (61.1)	
Totally three dose	9 (75.0)	3 (25.0)	
PDA (*n*) (%)	12 (54.5)	10 (45.5)	0.80
CLD (*n*) (%)	1 (33.3)	2 (66.7)	1.00
Death (*n*) (%)	6 (60.0)	4 (40.0)	0.74

BiPAP=Bi-level positive airway pressure, SiPAP=Sigh-positive airway pressure, SD=Standard deviation, IMV=Intermittent mandatory ventilation, IVH=Intra ventricular hemorrhage, PDA=Patent ductus arteriosus, CLD=Chronic lung disease

DISCUSSION

Most of the studies done in the field of noninvasive ventilation are done on the grounds of considering nCPAP as the treatment for the control group. Among the highlighted researches done based on the comparison of the subcategories of cycled-NIV, that is, SNIPPV when compared with nCPAP, we can refer to the study done by Bhandari *et al*. in two hospitals of the universities of Yale and San Diego, on 469 preterm infants weighing 1250 g or less who were treated with mechanical ventilation due to RDS. During the treatment, whenever the ventilator management of these newborns resulted in defined indications (FiO_2 ≤35%, rate = 15–25, positive end-expiratory pressure (PEEP) ≤5 cmH_2O, PIP ≤16 cmH_2O in order to maintain pH = 7.25–7.45, $PaCO_2$ = 40–55 mmHg, PaO_2 = 50–80 mmHg), the newborns were extubated and placed randomly into two groups of SNIPPV and nCPAP noninvasive respiratory support. The ventilator management (invasive and noninvasive) was done by infant star, whose synchronize mechanism was based on Graseby capsule placement over the abdomen. In this study, which was done during 2002–2004, after the extubation, for the newborns who were placed in the SNIPPV group (242 newborns), Inca (Infant Nasal CPAP Assembly) was placed, and respiratory support continued with the same rate as the invasive ventilation's; however, PIP was increased 2–4 cmH_2O, and PEEP was considered as equal or <6 cmH_2O, and FiO_2 was adjusted in a way to maintain the oxygen saturation in the range of 85–95%. In nCPAP group, after extubation, the newborns were treated by Inca with the continuous distending pressure (CDP) of equal to 4–6 cmH_2O, and FiO_2 was adjusted to maintain the oxygen saturation in the range of 85–95%. In case of the need for FiO_2 of <30%, the newborn was detached from the ventilator (respiratory support). The BPD

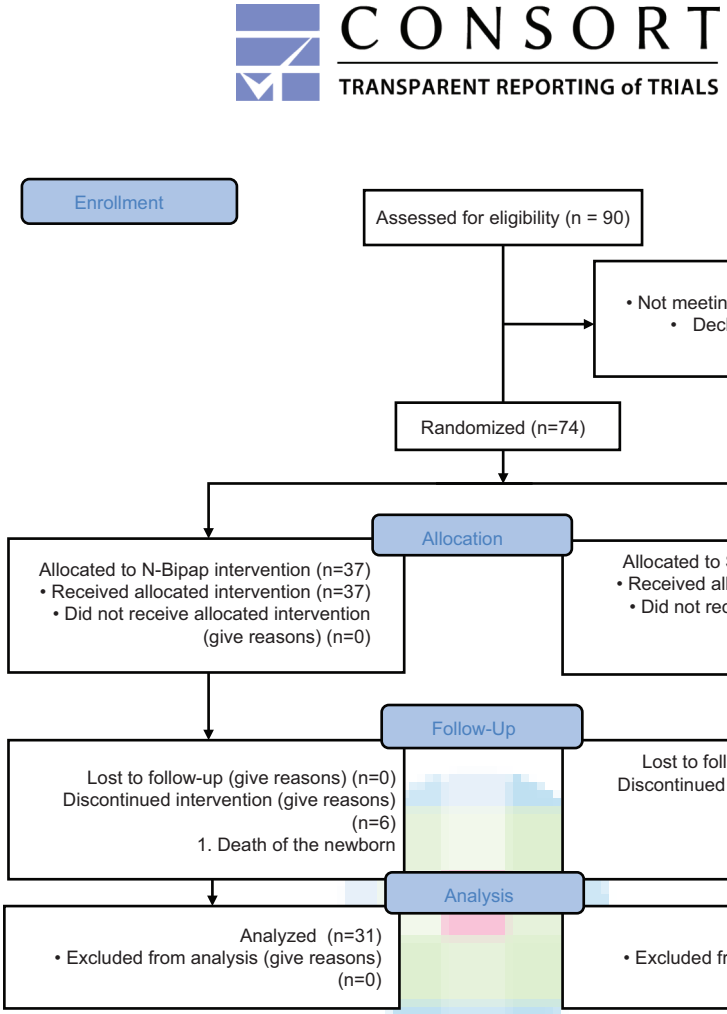

Figure 1: Preterm newborns weighing less than 1500 g affiliated with Respiratory Distress Syndrome who were admitted to the NICU at Alzahra Hospital from Sep 2011 to Jan 2013

incidence showed a significant difference in SNIPPV group, and the PVL incidence showed a significant difference in the nCPAP group.[18]

In another study done by Migliori *et al*., preterm infants (24–31 weeks) affiliated with RDS were treated by infant flow advance system after extubation (this system is capable of administering both nCPAP and N-BiPAP, however, the injector is of IFD type), and they recurrently experienced nCPAP and N-BiPAP. The study revealed that the newborns under the treatment with the N-BiPAP had a slower respiratory rate, and PCO_2 and they experienced higher in PO_2 levels.[19]

In a study done by Ali *et al*., preterm infants (weighing 500–1500 g) affiliated with RDS, who needed FiO_2 <50% under nCPAP, were treated with NI-PSV. In this study, they used Sechrist IV 200 SAVI ventilator and Inca injector, and the hardware system for synchronization was managed by respiratory inductance plethysmography (RIP); a system in which the ventilator is synchronized with the sum of transmitted signals from the placed loops over the area of abdomen and chest. For the pressure support, a balloon connected to a manometer was placed in the esophagus, which actually showed the change in the pressure of pleura. This mechanism, which was also referred to as esophageal pressure (P_{ES}), was used to adjust the level of pressure support in the proximal pressure line. During inspiration, *P* maximum (P_{max}) was considered up to 100–150% P_{ES}. Establishment of this system provides the researchers with the opportunity to assess flow volumes and minute ventilation in different situations. This study revealed that compared to the nCPAP group, the WOB decreased significantly in NI-PSV group.[20]

In a study which lasted from January 2007 to April 2008, Sai Sunil Kishore *et al.* compared to two respiratory management systems of nCPAP and NIPPV in newborns affiliated with RDS in an early intervention (within 2 h from birth). The newborns' gestational age ranged from 28 to 34 weeks, and if, during 6 h from birth, the newborns experienced downes score ≥4, they were treated randomly by nCPAP or NIPPV. Totally, 39 newborns were placed in an nCPAP group, and a maximum setup of 7 cmH_2O was considered as the CDP for FiO_2 ≤70%. A sum of 37 newborns were placed in NIPPV group, for which a primary

setup of rate = 40–50/min, Ti = 0.3–035 s, PEEP = 5 cmH_2O, and PIP = 15–16 cmH_2O was considered, and based on the gasometrical indications, the maximum setup was adjusted up to rate = 60/min, PEEP = 6 cmH_2O, PIP = 24–26 cmH_2O. In nCPAP group, the newborn was detached from respiratory support at CDP = 4 cmH_2O, FiO_2 ≤30%. In NIPPV group, the newborn was detached from respiratory support at rate = 30/min, PEEP = 4 cmH_2O, PIP = 14 cmH_2O, FiO_2 ≤30%. Compared to NIPPV group, the need for the reestablishment of invasive respiratory support during 48 h and also 1-week from the discontinuation of noninvasive respiratory support showed a significant increase in the nCPAP group.[21]

In a study done by Aghai *et al.*, 15 newborns under respiratory support with nCPAP (due to RDS, weighing between 823 g and 1819 g) with setup characteristics of CDP = 5 cmH_2O and FiO_2 <50%, were entered into noninvasive cycled respiratory support treatment (with infant star ventilator and the synchronized system involving pneumatic Star Sync capsule and Inca injector). SNIPPV noninvasive respiratory support was adjusted to PEEP = 5 cmH_2O, Ti = 35s, and PIP was administered at three different levels of 10, 12, and 14 cmH_2O; in all the above situations, the flow volume was calculated with RIP and calibrated and compared with face mask pneumotachography. Pressure changes in pleura which represent the transpulmonary pressure changes were assessed with a balloon placed in the esophagus. Using the data on pressure changes, compliance, elastic work of breath (WOB_E), inspiratory resistive work of breath ($RWOB_i$), and eventually the inspiratory work of breath (WOB_{insp}), which is the sum of $RWOB_i$ and WOB_E, were calculated. Resistive work of breath (RWOB) also results from the addition of $RWOB_i$ and $RWOB_E$. This study showed that compared to nCPAP group, RWOB decreased significantly in all conditions of SNIPPV; WOB_{insp} decreased significantly if only PIP was increased up to 12–14 cmH_2O (in SNIPPV); and WOB_E showed a significant decrease if only PIP = 14 cmH_2O.[22]

In a study done in 2009 by Lista *et al.*, N-BiPAP was used to treat RDS. However, as opposed to the study by Migliori, N-BiPAP was administered as the first line in RDS management, and the preterm newborns with gestational age of 28–34 weeks who demonstrated RDS indications were treated with noninvasive respiratory support in two groups of nCPAP with ventilator, and N-BiPAP with SiPAP (Viasys Healthcare). There were 20 newborns in each group, and the newborns in noninvasive-cyclic respiratory support (SiPAP) had significantly shorter hospitalization duration in NICU.[14]

In a study done by O'Brien *et al.* in 2012, the newborns affiliated with RDS who had weights of equal or <1250 g were treated with two kinds of noninvasive respiratory support at the time they were detached from the ventilator. The 69 newborns in the control group were treated with nCPAP, and the 67 newborns in the interventional group were treated with SiPAP. In nCPAP group, CDP and FiO_2 were defined as CDP = 5 cmH_2O and FiO_2 <0.3. In SiPAP group, EPAP, IPAP, and FiO_2 were defined as EPAP = 5 cmH_2O, IPAP = 8 cmH_2O, FiO_2 <0.3. Compared to the nCPAP group, the incidence of the need for recurrent intubation, intraventricular hemorrhage (grades 3 and 4), and mortality showed a decrease in SiPAP group; however, the decrease was not significant.[12]

CONCLUSIONS

It seems that this study is among a few current studies which aim at comparing two noninvasive ventilation systems for the newborns affiliated with RDS. The two systems in this study are categorized as cycled-NIV. This study could not find any significant difference for any of the outcomes between the groups; although the sample size for this study was low and more studies are needed in this field, due to the complicacy of working with SiPAP system, such as using Grasby capsule, and recurrent adjustment of flow by the operator to maintain the desired pressure for EPAP and IPAP, there seems to be no advantage in establishing SiPAP system over BiPAP, at least at the present time.

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