Original Article

Analysis and comparison of the effects of N-BiPAP and Bubble-CPAP in treatment of preterm newborns with the weight of below 1500 grams affiliated with respiratory distress syndrome: A randomised clinical trial

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Abstract

Background: Nowadays, establishment of nCPAP and surfactant administration is considered to be the first level of intervention for newborns engaged in the process of Respiratory Distress Syndrome (RDS). In order to decrease the side effects of the nCPAP management placed in noninvasive-non-cycled respiratory support. Noninvasive-cycled respiratory support mechanism have been developed such as N-BiPAP. Therefore, we compared N-BiPAP with Bubble-CPAP in a clinical trial.

Materials and Methods: This research was done as an on newborns weighing less than 1500 grams affiliated with RDS. A3 The total number of newborns was 70. Newborns were divided into two groups with the sample size of 35 patients in each, according to odd and even document numbers. One group was treated with N-BiPAP and the other with Bubble-CPAP. Patients were compared according to the length of treatment with noninvasive respiratory support, length of oxygen intake, number of surfactant doses administered, need for invasive mechanical ventilation, apnea, patent ductus arteriosus (PDA), chronic lung disease, intraventricular hemorrhage, pneumothorax, and death. Data was recorded and compared.

Results: The average duration for noninvasive respiratory support and the average time of need to complementary oxygen was not significantly different in both groups (P value > 0.05). Need for invasive ventilation, also chronic lung disease, intraventricular hemorrhage (IVH), pneumothorax, need for the next dose of surfactant, and the death rate did also have no meaningful difference. (P value > 0.05).

Conclusion: In this research N-BiPAP did not show any obvious clinical preference over the Bubble-CPAP in treatment of newborns weighing less than 1500 grams and affiliated with RDS.

Key Words: Bubble-CPAP, N-BiPAP, preterm newborn, respiratory distress syndrome

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INTRODUCTION

Diseases related to prematurity were considered to be the cause of 17% of death in 2003 in United States and it is estimated that almost half (49%) of this rate happened in newborns less than 1,000 grams, A4 with respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD) to

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be the most common causes of death in this group of newborns.[1]

Researches have proven that CPAP (Continuous Positive Airway Pressure) is effective in treatment of RDS with mechanisms such as increase in function residual capacity (FRC) that improves the level of PaO_2, improvement in lung compliance, better strength for airways, diaphragm function improvement, alveolar collapse avoidance, alveolar-arterial oxygen pressure gradient decrease (A-aDO2), intrapulmonary shunt decrease, obstructive and mixed apnea decrease, and surfactant preservation.[2]

Interface equipment for administration of noninvasive CPAP consists of full face mask, nasal mask, short and long nasal prongs.[3]

At the moment, A5 nasal continuous positive airway pressure (nCPAP) and surfactant administration is considered the first level of intervention in newborns with RDS, especially those with ELBW, but it necessitates the application of INSURE (Intubation, Surfactant, Extubation) for administration of the surfactant.[4-6]

Although, nCPAP is considered the standard care in treatment of the newborns with RDS, there are concerns about its side effects such as: High risk of air-leak syndrome (Pneumomediastinum, pneumothorax), lung over distention together with compliance decrease and therefore, increase in work of breathing, and also over increase in intrathoracic pressure, followed by venous return decrease to right heart, resulting in decrease of cardiac output.[7]

In order to decrease the unwanted side effects of the nCPAP intervention, which is considered noninvasive-non-cycled respiratory support, noninvasive-cycled respiratory support mechanisms have been developed during the last decade with the aim of noninvasive respiratory support with minimum side effects.[8-13] Noninvasive-cycled respiratory supports, as their technological indications differ according to functional basics, include a range of interventions, which covers N-BiPAP (Nasal bi-level Positive Airway Pressure). In BiPAP system, injector is just only based on IFD and the system creates two levels of PAP (Positive airway pressure) with flow control. The highest level of pressure, which is called IPAP (Inspiratory PAP) and the lowest level of pressure, which is called EPAP (Expiratory PAP), together with the sigh mechanism can revive the alveolus, improve FRC, avoid probable atelectasis, and finally decrease the work of breathing, and they can have potential advantages compared to non-cycled-NIV.[10] The aim of this research is to show probable clinical preference of N-BiPAP compared to Bubble-CPAP, in treatment of preterm newborn's respiratory distress syndrome.

MATERIALS AND METHODS

R2 The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences and informed consent was obtained from the parents after explaining the aim and protocol of the study. This research is a randomized clinical trial done on preterm newborns with 1,500 grams or less affiliated with the RDS at Alzahra and Beheshti hospitals under the authority of Isfahan Medical University from April 2011 to March 2012. Inclusion criteria includes newborns with weight of 1,500 grams or less, together with clinical symptoms of RDS (tachypnea, intercostal retraction, nasal flaring, granting) who needed fractional inspired oxygen more than 21%. Exclusion criteria includes congenital abnormality at birth and prenatal asphyxia (Apgar score less than 3 at minute 5, Cord pH less than 7, and cord bicarbonate less than 12) R3.[10] The sample size is 35 newborns in each group and sampling continued to reach the needed sample size of 35 in each group. In both groups at the time the newborn, needed FIO_2 more than 30% to maintain oxygen saturation in the range of 90% to 95% in the right hand using INSURE, he would be treated by surfactant administration of Curosurf kind with the dose of 200 mg/Kg (2.5 mL/kg), (all newborns in both groups received the first dose of surfactant), and if the newborn continued to need FIO_2 more than 40% in order to maintain oxygen saturation in an acceptable range 12 h after the last dose of surfactant, another dose of Curosurf with the dose of 100 mg/Kg (1.25 mL/kg) was administrated and in the case of need, the treatment period (maximum 3 doses) was completed.[13,14] Newborns in N-BiPAP group were first treated by IFD Injector (Viasays Healthcare) with appropriate nasal prongs, then a positive pressure of 4 cm H_2O for EPAP and a positive pressure of 8 cm H_2O for about 0.5 second for IPAP was administered using Non-invasive respiratory support system Fabian nCPAP (Acutronic Medical System AG Swiss) and a pressure exchange rate of 30/min was considered for the newborn.[13] CBG (capillary blood gas) test was taken from the newborns right after the surfactant administration and every 12 h afterwards. If the PCO_2 was less than 65 mmHg and pH was over 7.25, first pressure exchange rate was lowered to 15/min, then IPAP was decreased to the level of 6 cm H_2O, and FIO_2 was also decreased gradually according to oxygen saturation rate, and at IPAP = 6 cm H_2O, EPAP = 4 cm H_2O and $FIO_2 < 30\%$ the newborn was weaned.[14] Newborns who were placed in Bubble-CPAP

group were treated by respiratory support with nCPAP by Bubble-CPAP BC161 (Infant Delivery System, Fisher and Paykel, Auckland, New Zealand). First, in order to achieve CDP = 6 cm H_2O, end of expiratory arm was drown in the chamber at 6 cm and flow was increased gradually to observe steady bubbles, in both inspiration and expiration. IF oxygen saturation stayed in an appropriate range for a period of about 4 h, CDP was decreased each time about 1 to 2 cm H_2O, and at CDP = 4 cm H_2O with $FIO_2 < 30\%$ the newborn was separated from nCPAP respiratory support.[15] If the following occurred, the newborn would be treated by invasive mechanical treatment: Inability to maintain appropriate ventilation and occurred respiratory failure (In N-BiPAP group to have $PCO_2 > 65$ mm Hg and PH < 7.2, although EPAP = 4 cm H_2O, IPAP = 8 cm H_2O, pressure exchange rate = 30/min and T_{high} = 0.5-0.7, and for Bubble-CPAP group to have the CDP = 8 cm H_2O), more than three times apnea in an hour that needs stimulation or bag-mask ventilation, and need to maintain $FIO_2 > 75\%$ to keep the level of oxygen saturation in the right hand in the range of 90% to 95%.[14-16]

In the first 48 h from birth, Echocardiogram was taken from newborns, in both groups to check for the PDA. Also in both groups, brain ultrasonographic were taken to check for Intraventricular hemorrhage (IVH), in day 3, 7, and 14 from birth. The duration of the non-invasive respiratory support, administered doses of surfactant, need for mechanical ventilation, duration of oxygen intake (after separation from non-invasive respiratory support), chronic lung disease that define need to receive supplementary oxygen for more than 28 days after birth,[4] Pneumothorax, and apnea recurrence rate was recorded in the questionnaire for Demographic Characteristics.

Collecting and analysis of data

The data was collected in a checklist and was analyzed with independent T-test, Pearson Correlation test, and Chi-square test using SPSS version 18.

RESULTS

From 77 newborns entering the research, 4 were excluded because of Asphyxia, 2 for mothers with intra-amniotic infection, and one for Congenital Malformation. From the 70 remaining newborns, 35 were placed in Bubble-CPAP group, and the other 35 in N-BiPAP group.

Demographic characteristics of newborns are shown in Table 1, and no significant difference was observed between the two groups in these variables.

In Bubble-CPAP group, 29 newborns (82.9%) were born with caesarian route and 6 (17.1%) were born with vaginal route, and in N-BiPAP group, 28 (80.0%) were born with caesarian route, and 7 (20.0%) were born with vaginal route, which did not show any statistical difference (*P* value = 0.75). Premature rapture of membrane happened to 7 (20.0%) of the Bubble-CPAP group, and to 6 (17.1%) newborns in N-BiPAP group, which had no significant difference (*P* value = 0.75). Steroid had been administered for 32 (91/4%) of mothers in Bubble-CPAP, while the number of mothers receiving steroid in N-BiPAP group was 31 (88/6%) (*P* value = 0.69). The reason for premature delivery in Bubble-CPAP and N-BiPAP group was 14 (40.0%) and 14 (40.0%) Preeclampsia, 9 (25.7%) and 8 (22.9%) Premature Labor, 7 (20.0%) and 6 (17.1%) premature rapture of the membrane, and 5 (14/3%) and 7 (20.0%) other reasons (fatal bradycardia, non-reassuring NST, cervical insufficiency, oligohydramnios, vaginal bleeding, and intra uterine growth retardation), respectively, which is not statistically significant, (*P* value = 0.92).

Table 1: Demographic characteristics of newborns in two groups

	Bubble-CPAP[1] (%)	N-BiPAP[2] (%)	*P* value[3]
Sex			
Female	11 (31.4)	17 (48.6)	0.14
Male	24 (68.6)	18 (51.4)	
Gestational age (week) Mean (SD[4])	28.32 (1.99)	29.35 (2.65)	0.06
Birth weight (gram) Mean (SD)	1090.57 (258.21)	1129.14 (279.86)	0.55
First minute Apgar Mean (SD)	4.63 (2.06)	5.57 (1.52)	0.03
Fifth minute Apgar Mean (SD)	7.03 (1.79)	7.57 (1.01)	0.12

[1]Bubble continuous positive airway pressure, [2]Nasal Bi-level positive airway pressure, [3]*P* value for these criteria must be less than 0.05, [4]Standard deviation

Table 2: Respiratory and clinical outcomes in two groups

	Bubble-CPAP[1] (%)	N-BiPAP[2] (%)	*P* value[3]
Length of non-invasive support (h; mean (SD[4]))	41.08 (19.08)	36.86 (11.33)	0.26
O2 dependency (h; mean (SD))	59.31 (38.61)	54.06 (27.85)	0.52
Apnea	13 (37.1)	10 (28.6)	0.44
Mechanical ventilation	9 (25.7)	5 (14.3)	0.23
Chronic lung disease (CLD)	2 (7.1)	1 (3.3)	0.51
Intraventricular hemorrhage	7 (20)	6 (17.1)	0.75
Grade 1	1 (14.3)	2 (33.3)	
Grade 2	3 (42.9)	4 (66.7)	
Grade 3	2 (28.6)	0 (0)	0.33
Grade 4	1 (14.3)	0 (0)	
Pneumothorax	3 (8.6)	1 (2.9)	0.30
Repeated surfactant	19 (54.3)	16 (45.7)	0.47
Totally 2 doses administered	8 (42.1)	7 (43.8)	0.92
Totally 3 doses administered	11 (57.9)	9 (56.2)	
Patent ductus arteriosus (PDA)	10 (28.6)	11 (31.4)	0.79
Death	7 (20)	5 (14.3)	0.52

[1]Bubble continuous positive airway pressure, [2]Nasal Bi-level positive airway pressure, [3]*P* value for these criteria must be less than 0.05, [4]Standard deviation

In Table 2, outcomes are compared between two groups. In order to review and compare the duration of non-invasive support and oxygen therapy in both groups, controlling the Apgar score in min 1, we used co-variance analysis. Adjusting this variable, the difference of duration for non-invasive support in both groups was not significant. Oxygen therapy duration had also no significant statistical difference, (*P* value = 0.70). The average duration of supportive ventilation in Bubble-CPAP was 36.44 (16.79) h and in N-BiPAP it it was 19.60 (11.41), which showed no statistical difference (*P* value = 0.07).

DISCUSSION

In our study, the duration of non-invasive respiratory support in newborns treated with N-BiPAP was shorter than the newborns in Bubble-CPAP Group. The duration of need for oxygen supplement after weaning also showed a decrease in N-BiPAP group compared to Bubble-CPAP. Pneumothorax incidence was less than half in N-BiPAP than in Bubble-CPAP group. The incidence of need for administration of the next dose of surfactant, PDA, IVH, and death in the group treated with Bubble-CPAP was higher than the N-BiPAP group, though this difference did not have any meaning.

This study could not reach any meaningful difference in non-invasive respiratory support in newborns affiliated with RDS, under treatment by N-BiPAP in comparison with newborns treated with Bubble-CPAP. However, in the study by Lista *et al.* the newborns treated by N-BiPAP showed a meaningful decrease in duration of respiratory support than newborns in nCPAP group.[13] We should note that in Lista's study, the gestational age of newborns was considered to be 28-34 weeks, but the gestational age of newborns in this study was considered to be 26-33 weeks. A11 Considering this fact, we should say that in Lista's study, the average gestational age of newborns is higher, so it might have had an effect on the decrease of the severity of RDS disease in these newborns. On the other hand, Lista *et al.* used Ventilator derived CPAP to administer nCPAP.

In a research done by MIgliori *et al.*, newborns affiliated with RDS showed a meaningful decrease in need for FIO_2 using N-BiPAP rather than nCPAP. A12 The increase in FIO_2 can be accompanied with some side effects for e.g. Retinopathy of prematurity, and the surfactant damage, development of chronic lung disease. So, it is obvious that the decrease in FIO_2 will lead to the decrease of these side effects.

A reason for the apnea incidence in newborns treated with continuous distending pressure (CDP), was increase in work of breathing. In a study done by Ali *et al.*, they discovered that the work of breathing in newborns treated with non-Invasive pressure support ventilation (NI-PSV) showed a decrease compared to newborns treated with nCPAP.[17] In the study done by Aghayi and *et al.*, there was also a decrease in work of breathing in newborns treated with SNIPPV (Synchronized nasal intermittent positive pressure ventilation) compared to nCPAP group.[18] A13 In two separate studies, Ali *et al.*, and Aghayi *et al.*, like our study, put a group in a non-cyclic non-invasive respiratory support, in comparison with the other group being treated with cyclic non-invasive respiratory support, the decrease in apnea incidence in cyclic non-invasive respiratory support group was obvious, but due to the low number of the sample size in our study, this decrease could not become meaningful. In our study, apnea incidence shows an increase in Bubble-CPAP than N-BiPAP group; however this difference is not significant.

In a study done by Kishore and *et al.*, the need for Invasive mechanical ventilation in preterm newborns affiliated with RDS treated with NIPPV (Nasal intermittent positive pressure ventilation) was less common than the nCPAP group. However in his study, the gestational age for preterm newborns was considered 28 to 34 weeks of gestation.[12] In this study, mechanical ventilation in N-BiPAP group had a lower incidence than Bubble-CPAP, but the difference was not significant. A14 It seems that the lack of sufficient sample size in our study caused insignificance of meaning in our study.

Bhandari and *et al.*, showed in a study that the CLD incidence in newborns affiliated with RDS with weights lower than 1,250 grams, who were treated with SNIPPV was lower than those newborns with the same conditions treated with nCPAP.[1] However, our study did not show such result.

No similar studies were found on the issues of pneumothorax incidence, the need for administration of the second dose of surfactant, PDA, IVH, and death.

Studies done on potential benefits of N-BiPAP seem to be limited at the moment. However, considering the significant results of this study, it can eventually initiate further studies in this field.

CONCLUSIONS

Our study showed a decrease in duration of treatment and need for oxygen supplement in N-BiPAP group rather than Bubble-CPAP, R5 though this decrease was meaningless. Apnea, pneumothorax, need to

administer the second dose of surfactant, PDA, IVH, and death R5 were insignificantly lower in N-BiPAP group compared to Bubble-CPAP group. Considering the lack of meaning for these criteria, and regarding the potential benefits of noninvasive respiratory supports of Cycled type in treatment of newborns, we suggest that more studies be done in the similar field with larger sample sizes, since the results are more probable to get a statistical meaning with larger sample sizes.

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