EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 9
58-64
Year: 2018

NASAL/BUBBLE CPAP VERSUS MECHANICAL VENTILATION FOR RESPIRATORY SUPPORT IN PRETERM INFANTS AT BIRTH

Fatima Mohsen, Sirin Mneimneh*, Amal Naous and Mariam Rajab

*Makassed General Hospital Department of Pediatrics, Beirut, Lebanon.

***Corresponding Author: Dr. Sirin Mneimneh**
Makassed General Hospital Department of Pediatrics, Beirut, Lebanon.

Article Received on 14/07/2018 **Article Revised on 03/08/2018** **Article Accepted on 23/08/2018**

ABSTRACT

Background: Preterm neonates are at risk of respiratory distress syndrome (RDS) and require mechanical ventilation to keep them alive. However, there are complications associated with mechanical ventilation which are mostly iatrogenic. Of these, Ventilator-Induced Lung Injury (VILI) has long been recognized as a contributor to the development of bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD). There has been increased interest in continuous positive airway pressure (CPAP) as a primary 'gentler' mode of respiratory support in RDS to improve mortality and reduce the occurrence of long-term respiratory morbidity. **Methods:** We performed a retrospective study, involving neonates who were born between 24 weeks 0 days and 36 weeks 6 days of gestation. Neonates were managed by CPAP or mechanical ventilation strategy. The primary outcomes were death, bronchopulmonary dysplasia (BPD), and duration of hospital stay. The secondary outcomes were patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), and pneumothorax. **Results:** A total of 250 neonates were enrolled in the study. The rates of the primary outcomes (death, BPD, and duration of hospital stay) and part of the secondary outcomes (PDA and NEC) were statistically significant between the two strategies (CPAP and mechanical ventilation). Pneumothorax didn't show any statistically significance difference between the two groups. Neonates who were managed by CPAP strategy, showed lower incidence of BPD (P-value= 0.046), PDA (P-value=0.016), NEC (P-value=0.001), and death (P-value <0.0001), and shorter duration of hospital stay (P-value<0.0001). **Conclusion:** The result of this study supports consideration of CPAP as an alternative strategy to intubation and mechanical ventilation in preterm neonates for respiratory support at birth.

KEYWORDS: Preterm neonates; CPAP; Mechanical ventilation.

INTRODUCTION

Neonatal respiratory failure is a serious clinical problem associated with high morbidity, mortality, and cost.[1,5] Although life-saving, invasive mechanical ventilation in preterm neonates is a major risk factor for the development of bronchopulmonary dysplasia (BPD) and Ventilator-Induced Lung Injury (VILI). These concerns have prompted neonatologist to use non-invasive modes of ventilation, and this has been increasingly gaining acceptance in most neonatal units.[6]

Exogenous surfactant replacement therapy and mechanical ventilation (MV) still remain the 'standard of care' while treating preterm infants with respiratory failure. Depending on the patient's condition, mechanical ventilation can help support or completely control breathing. However, this requires endotracheal intubation - an invasive procedure associated with complications.[7]

A study in the United States reports a mechanical ventilation rate of 18 per 1,000 live births and the total cost of $4.4 billion for treating respiratory failure.[8,10]

CPAP, or continuous positive airway pressure, refers to spontaneous ventilation with a positive airway pressure being maintained throughout the whole respiratory cycle. CPAP primarily improves oxygenation by increasing functional residual capacity, and may increase lung compliance and decrease the work of breathing. PEEP/CPAP may be applied using endotracheal tubes, nasal masks or prongs, or face masks or chambers to treat a wide range of adult and pediatric respiratory disorders.[11]

The old practice guidelines (American Academy of Pediatrics 2008) in neonatology recommend administration of surfactant at or soon after birth in preterm infants with respiratory distress syndrome (RDS).[12] However, recent multicenter randomized controlled trials indicate that nasal continuous positive airway pressure (CPAP) may be an effective alternative to prophylactic or early surfactant administration. More studies are needed looking at optimizing CPAP and maximizing its benefits while giving us device specific results and effective CPAP treatment protocols.[13]

The purpose of the study was to support the use of CPAP instead of mechanical ventilation in preterm infants, owing to lesser rate of morbidity and mortality in preterm infants ventilated by CPAP device after birth.

METHODS

It is a retrospective study that compared the strategy of respiratory support at birth with CPAP device versus invasive intubation and mechanical ventilation.

Infants were eligible for inclusion in the study if:

1. Neonates were born between 24 weeks 0 days and 36 weeks 6 days of gestation at birth according to the best obstetrical estimate
2. Neonates were born without known malformations (congenital diaphragmatic hernia, tracheo-esophageal fistula, and cleft lip/palate)
3. A decision had been made to provide full resuscitation for them

Population

Sample size was 250 neonates in neonatal intensive care unit. Of these neonates, 109 were in the CPAP group and 141 in the MV group. They were distributed according to gender (male/female), gestational age, and birth weight.

Preterm neonates were subdivided into three subgroups according to the gestational age[14]:

1. Extremely preterm (24 - 27+6 weeks)
2. Very preterm (28 - 31+6 weeks)
3. Moderate to late preterm (32 - 36+6 weeks)

Neonates were also classified according to their birth weight[15] into four subgroups:

1. Extremely low birth weight (below 1000 grams)
2. Very low birth weight (between 1000-1499 grams)
3. Low birth weight (between 1500-2499 grams)
4. Weight above 2000 grams

Maternal group B streptococcus (GBS) vaginal culture was recorded as positive or negative, and we calculated the number of mothers treated by antimicrobial therapy, also whether mothers received steroid antenatally.

Apgar score at 1 minute after birth was denoted as a score above 6 points and below or equal to 6 points. Chest X-ray finding recorded as normal lungs or hyaline membrane disease.

CPAP group

It included 109 neonates out of total of 250 neonates. CPAP was administered by means of nasal or bubble device, and ventilation with positive end-expiratory pressure (PEEP) (at a recommended pressure of 4-5 cm of water) was used.

Mechanical Ventilation group

It included 141 out of 250 neonates. Endotracheal intubation was done, followed by the administration of 1 or 2 doses of surfactant, according to the chest-x-ray findings (normal lungs or hyaline membrane disease and its severity), and then the infant was attached to mechanical ventilation machine. The pressures used were PIP (peak inspiratory pressure) that ranged between 12-22 cm of water and PEEP (positive end-expiratory pressure) that ranged between 4-5 cm of water.

Outcomes

The primary outcomes: Death, BPD, and Duration of hospital stay.

Broncho-pulmonary dysplasia is a form of chronic lung disease that develops in preterm neonates treated with positive-pressure ventilation and it's defined as the requirement of supplemental oxygen at corrected age of 36 weeks.[16]

The secondary outcomes: PDA, NEC, and Pneumothorax.

Statistical Analysis

Categorical variables were presented as number and percent, whereas continuous ones were presented as mean and standard deviation.

Bivariate analysis was carried out by using the chi square for comparing categorical variables, whereas continuous ones were compared using the Student's t-test.

Multivariate analyses were carried out by multivariate linear regression for continuous outcomes or multivariate logistic regression for categorical variables.

Variables were controlled for infant gestational age, birth weight, APGAR score, and antenatal steroid administration.

Results were presented as odds ratio (OR) and 95% confidence interval (95% CI) for logistic regression analysis, whereas the coefficient and 95% CI were presented for linear regression analysis.

The Statistical Package for Social Sciences (SPSS, version 21) program was used for data entry, management, and analysis. Statistical significance was indicated at 0.05.

RESULTS

From January 2010 through April 2016, a total of 250 infants were enrolled in our study, of whom 109 infants were in the CPAP group and 141 infants were in the mechanical ventilation group (Table 1).

Extremely preterm infants were 3 infants (2.8%) in the CPAP group and 31 (22%) in the MV group. Very preterm infants were 14 infants (12.8%) in CPAP and 54 infants (38.3%) in MV group. Moderate to late preterm infants were 92 infants (84.4%) in CPAP and 56 infants (39.7%) in MV group.

Extremely low birth weight infants were 3 infants (2.8%) in the CPAP group and 35 infants (24.8%) in the MV group. Very low birth weight were 9 infants (8.3%) in CPAP and 48 infants (34.0%) in MV group. Low birth weight were 49 infants (45.0%) in CPAP and 46 infants (32.6%) in MV group. Infants with weight above 2000 grams were 48 infants (44.0%) in CPAP and 12 infants (8.5%) in MV group.

GBS culture was positive in 13.3% of mothers whom infants were in CPAP group (treated by antimicrobial therapy in 31.2%) and it was positive in 10.0% in MV group (treated in 23.3%). Also, 43.1% of infants in CPAP group were born to mothers who received steroid antenatally, versus 61.7% in the MV group.

92.7% of infants in CPAP group were born with 1 minute Apgar score above 6 points, and 7.3% Apgar score below or equal to 6 points. In the MV group, 50.4% had Apgar score above 6 points and 49.6% were below or equal to 6 points.

Chest X-ray showed normal lungs in 98.2% of infants in CPAP group and 46.1% in MV group, and it showed hyaline membrane disease picture in 1.8% of CPAP group and 51.2% of the MV group.

Primary Outcome (tables 2, 3 and 4)

As regarding preterm infants (born between 24 to 36+6 weeks of gestation), the percentage of BPD was 0.9% in the group which was managed by CPAP (first group) versus 6.4% in the intubation and mechanical ventilation (second) group; indicating a statistically significant difference between the two groups (P-value=0.046), odds ratio 1.13, 95% confidence interval 0.086-14.81.

The percentage of death was 0.9% in the first group versus 19.9% in the second group; indicating a significant difference between the two groups (P-value<0.0001), odds ratio 5.84, 95% confidence interval 0.68-50.54.

The duration of hospital stay was 12.77 (SD=11.88) in the first group and 30.01 (SD=21.86) in the second group; indicating a statistically significant difference between the two groups (P-value<0.0001), coefficient 5.97, 95% confidence interval 1.10-10.84.

As regarding preterm infants (born between 24 to 27+6 weeks of gestation), the percentage of BPD was 33.3% in the group which was managed by CPAP (first group) versus 16.1% in the intubation and mechanical ventilation (second group); without statistically significant difference between the two groups (P-value=0.45).

The percentage of death was 0.0% in the group which was managed by CPAP (first group) versus 54.8% in the intubation and mechanical ventilation (second group); without statistically significant difference between the two groups (P-value=0.23).

Secondary Outcome (tables 2 and 4)

As regarding preterm infants(born between 24 to 36+6 weeks of gestation), the percentage of PDA was 1.8% in the group which was managed by CPAP (first group) versus 9.9% in the intubation and mechanical ventilation (second) group; indicating a statistically significant difference between the two groups (P-value=0.016), odds ratio 2.37, 95% confidence interval 0.42-13.52.

The percentage of NEC was 1.8% in the first group versus 13.5% in the second group; indicating a statistically significant difference between the two groups (P-value= 0.001), odds ratio 3.28, 95% confidence interval 0.63-16.96.

The percentage of pneumothorax was 1.8% in the first group versus 5.0% in the second group; but there was no statistically significant difference between the two groups (P-value=0.31), odds ratio 3.27, 95% confidence interval 0.54-19.62.

7 infants out of 109 infants (6.4%) in the CPAP group failed this strategy (they had increase in their respiratory distress and subsequently intubated and mechanically ventilated).

Table 1: Patients' demographic characteristics.

Variables		CPAP n (%)	Mechanical Ventilation (%)n	p-value
Gender	Male	67 (61.5%)	78 (55.3%)	0.37
	Female	42 (38.5%)	63 (44.7%)	
Gestational age (week)	24 - 27+6	3 (2.8%)	31 (22.0%)	<0.0001
	28 - 31+6	14 (12.8%)	54 (38.3%)	
	32 - 36+6	92 (84.4%)	56 (39.7%)	
Birth weight (gram)	< 1000	3 (2.8%)	35 (24.8%)	<0.0001
	1000 – 1499	9 (8.3%)	48 (34.0%)	
	1500- 2499	49 (45.0%)	46 (32.6%)	
	>=2500	48 (44.0%)	12 (8.5%)	
Maternal GBS status	Positive	8 (13.3%)	4 (10.0%)	0.76
GBS maternal infection	Treated	15 (31.2%)	17 (23.3%)	0.40
	Not treated	33 (68.8%)	56 (76.7%)	
Antenatal steroid administration	No	62 (56.9%)	54 (38.3%)	0.005
	Yes	47 (43.1%)	87 (61.7%)	
Apgar score at t 1 min	< or = 6	8 (7.3%)	70 (49.6%)	<0.0001
	>6	101 (92.7%)	71 (50.4%)	
Chest Xray result	Normal	107 (98.2%)	65 (46.1%)	<0.0001
	HMD	2 (1.8%)	72 (51.2%)	

Table 2: Comparison of outcomes between CPAP and Mechanical ventilation.

		CPAP n (%)	Mechanical Ventilation n(%)	P-value
Primary outcome	BPD	1 (0.9%)	9 (6.4%)	0.046
	Death	1 (0.9%)	28 (19.9%)	<0.0001
	Duration of hospital stay (days) (mean±SD)	12.77 (SD=11.88)	30.01 (SD=21.86)	<0.0001
Secondary outcome	PDA	2 (1.8%)	14 (9.9%)	0.016
	NEC	2 (1.8%)	19 (13.5%)	0.001
	Pneumothorax	2 (1.8%)	7 (5.0%)	0.31

Table 3: Comparison of outcomes between CPAP and Mechanical ventilation in extremely preterm infants.

24 – 27+6 weeks (34/250 infant)	CPAP (3 infants) n (%)	MV (31 infant) n (%)	P-value
BPD	1 (33.3%)	5 (16.1%)	0.45
Death	0 (0.0%)	17 (54.8%)	0.23

Table 4: Multivariate analysis.

	Odds Ratio	95% CI	P-value
BPD	1.13	0.086 – 14.81	0.93
Death	5.84	0.68 – 50.54	0.11
PDA	2.37	0.42 – 13.52	0.33
NEC	3.28	0.63 – 16.96	0.16
Pneumothorax	3.27	0.54 – 19.62	0.20
	Coefficient	**95% CI**	**P-value**
Duration of hospital stay	5.97	1.10 – 10.84	0.016

DICUSSION

Because of possible complications of endotracheal intubation and mechanical ventilation, including laryngeal and tracheal injury, ventilator induced lung injury and subsequent increase in the incidence of BPD and its severity, and increased risk of nosocomial pneumonia and sepsis; using non-invasive modes of respiratory care could have many advantages for preterm infants.[17] The effects of CPAP includes an increase in functional residual capacity, thus improving arterial pressure of oxygen (PaO2), decreasing airway resistance, reducing obstructive apnea, and stabilizing the chest wall with reduction of its distortion.[18]

There were no statistically significant differences between the two treatment groups with respect to the infant gender (P-value=0.37) and maternal GBS status (P-value=0.76) and its treatment (P-value=0.4). There were statistically significant differences with respect to infant birth weight (P-value<0.0001), gestational age (P-value<0.0001), Apgar score at 1 minute (P-value<0.0001), chest-X-ray finding (P-value<0.0001), and maternal steroid administration (P-value=0.005).

In our study, there was a statistically significant difference between a strategy of nasal/bubble CPAP and a strategy of intubation with mechanical ventilation and surfactant administration with respect to the rate of the composite the primary outcomes (death, BPD, and the duration of hospital stay) [P-value<0.0001, P-value=0.046, and P-value<0.0001, respectively], and the secondary outcomes (PDA and NEC) [P-value=0.016 and P-value=0.001 respectively]; but there was no statistically significant difference regarding pneumothorax as an outcome (P-value=0.31).

But, when we studied the extremely preterm infants as a single group, the rate of BPD and death outcomes weren't statistically significant between the two groups [P-value=0.45 and P-value=0.23 respectively].

In our study, only 7 infants out of 109 infants (6.4%) in the CPAP group showed failure in improvement when ventilated by CPAP device and they required intubation and mechanical ventilation, while 102 infants (93.6%) become free of respiratory distress; so the failure rate was 6.4% only. This was consistent with the results of the study carried out by Tagare et al[19] and Lee.[20] Our results were inconsistent with the studies done by Morley[21] and Pillow[22] demonstrated that CPAP increases the respiratory effort in the neonate more so than MV and showed high failure rate in CPAP group.

Our analysis demonstrated that the risk of death, BPD, PDA, and NEC were statistically significant and higher in the group treated by mechanical ventilation, and the duration of hospitalization was also longer, but there was no statistically significant risk of pneumothorax.

CPAP strategy in our institution showed advantage in terms of survival and chronic lung disease (BPD). While in the COIN trial, which included 610 infants of between 25 to 28 weeks gestation were randomized to receive either early CPAP or Intubation and Ventilation without surfactant (CPAPor Intubation (COIN Trial)), CPAP did not show any advantage in terms of survival or chronic lung disease (CLD) at the time of discharge.[23]

Another study is the SUPPORT trial (Surfactant Positive Pressure and Pulse Oximetry Randomised Trial) which enrolled 1316 infants born between 24 to 27weeks gestation to receive either early CPAP in the delivery room without any surfactant (CPAP group) or intubation and surfactant treatment within one hour after birth (ventilation group). The primary outcome of death or chronic lung disease did not differ between the two groups (47% in CPAP group *versus* 51.0% in ventilation group).[24]

A lower percentage of pneumothorax in the CPAP group has been indicated but it wasn't statistically significant. Moreover in the COIN trial, babies in CPAP group had somewhat higher incidence of pneumothorax as compared to ventilation group.[23]

There was also no difference in the incidence of pneumothorax in the SUPPORT trial.[24]

We noticed that the majority of newborns with lower gestational age (at entry to the study) and lower 1 minute Apgar score were present in the MV group; so the demographic characteristics were not identical between the two groups. Thus, the MV group represented a high risk group (extremely preterm infants with low Apgar score at birth), contributing to high mortality and high need for early intubation in the delivery room. Therefore, the gestational age of the infant (below 28 weeks) and his Apgar score at birth (below or equal to 6) could increase the risk of morbidity and mortality in the MV group.

Despite the finding of hyaline membrane disease picture (denoting surfactant deficiency) on chest imaging in the MV group in high percentage of infants; these infants received surfactant (1 or 2 doses) after being intubated; so the surfactant deficiency was corrected and lungs were cleared on repeated imaging, becoming like the clear lungs of infants in CPAP group. So lung pathology at birth (hyaline membrane disease) could not affected the results of the study.

Death was higher in the MV group because of the high risk of the adverse neonatal outcomes in these infants (BPD, PDA, and NEC) when compared to CPAP group; in addition to the un-modifiable risk factors for mortality in these infants (including lower gestational age and lower birth weight).

BPD is mainly caused by lung injury from intubation and mechanical ventilation, so it occurred more in the MV group.

The duration of hospital stay was shorter in CPAP group, since majority of infants in this group didn’t developed NEC; thus tolerated feeding and reached full feed with adequate caloric intake more rapidly and discharged earlier from the hospital. Unlike, the infants in the MV group who required cessation of feeding several times due to feeding intolerance caused by NEC, leading to longer duration of hospitalization.

Occasional impingement of the expiratory tubing exit of CPAP device by mattress, coverings, or walls of neonates warmers is of concern because of risk for obstruction and pneumothorax; especially the nasal CPAP[25], this may explain the risk of pneumothorax found in our study in the CPAP group. Higher percentage (but not statistically significant) of pneumothorax occurred in the MV group, probably due to the use of high peak inspiratory pressure (PIP) on mechanical ventilation.

It is essential to remember that ninety percent of babies with NEC are preterm. NEC typically affects babies born before 32 weeks gestation, but it can occur in full-term infants who have health problems. The incidence of NEC is inversely proportional to birth weight.[26] We noticed in our study, the infants in the MV group were aged less than 32 weeks of gestation and had a weight less than 2 kilogram. While the infants in the CPAP group were older than 32 weeks of gestation and weigh more than 2 Kilogram. Therefore, NEC might occurred more in the MV group due to lower gestational age and lower weight of these infants, and not solely due to mechanical ventilation itself.

In summary, we found a statistically significant difference in the primary outcomes (death, bronchopulmonary dysplasia, and duration of hospital stay); between preterm infants (24 – 36+6 weeks) managed by the CPAP strategy and those managed by mechanical ventilation strategy (with surfactant replacement), regarding respiratory support in preterm infants at birth. In which the infants in the CPAP group had lower risk of death and BDP, and shorter duration of hospital stay (P-value<0.0001, P-value=0.046, P-value<0.0001, respectively), but not in extremely preterm infants (24 – 27+6 weeks).

In secondary analyses, the CPAP strategy, as compared with mechanical ventilation strategy, resulted in a lower rate and lesser risk of any adverse neonatal outcome including PDA and NEC (P-value=0.016 and P-value=0.001 respectively).

The main limitations of this study are the following:

1. Retrospective study
2. Small sample size (250 infants)
3. Population was selected from one center
4. Imbalance in the basic demographic characteristics that could alter the results of the study

CONCLUSION

These data supports the consideration of CPAP as an alternative strategy to routine intubation - surfactant administration and mechanical ventilation when managing preterm infants at birth.

REFERENCES

1. Chami M, Geoffray A. Pulmonary sequelae of prematurity: radiological manifestations. Pediatr Pulmonol Suppl., 1997; 16: 51.
2. Chye JK, Gray PH. Rehospitalization and growth of infants with bronchopulmonary dysplasia: a matched control study. J Paediatr Child Health, 1995; 31(2): 105–11.
3. Collaborative UK, Trial Group. ECMO. UK collaborative randomized trial of neonatal extracorporeal membrane oxygenation. Lancet, 1996; 348(9020): 75–82.
4. Economic outcome for intensive care of infants of birthweight 500–999 g born in Victoria in the post surfactant era. The Victorian Infant Collaborative Study Group. J Paediatr Child Health, 1997; 33(3): 202–8.
5. Vaucher YE, Dudell GG, Bejar R, Gist K. Predictors of early childhood outcome in candidates for extracorporeal membrane oxygenation. J Pediatr, 1996; 128(1): 109–17.
6. Jobe AH. The new bronchopulmonary dysplasia. Curr Opin Pediatr, 2011; 23: 167–72.
7. Soll RF. Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev., 2000; 2: CD000511.
8. Angus DC, Linde-Zwirble WT, Clermont G, et al. Epidemiology of neonatal respiratory failure in the United States. *Am* J Respir Crit Care Med., 2001; 164(7): 1154–60.
9. Jobe AH. The new bronchopulmonary dysplasia. Curr Opin Pediatr., 2011; 23: 167–72.
10. Davis PG, Morley CJ, Owen LS. Non-invasive respiratory support of preterm neonates with respiratory distress: Continuous positive airway pressure and nasal intermittent positive pressure ventilation. Sem Fetal Neonatal Med., 2009; 14(1): 14–20.
11. Duncan AW, Oh TE, Hillman DR. PEEP and CPAP, Anaesth Intensive Care, 1986 Aug; 14(3): 236-50.
12. Engle WA; American Academy of Pediatrics Committee on Fetus and Newborn. Surfactant replacement therapy for respiratory distress in the preterm and term neonate. Pediatrics, 2008; 121(2): 419–432.
13. Sandri F, Ancora G, Lanzoni A, et al. Prophylactic nasal continuous positive airways pressure in newborns of 28-31 weeks gestation: multicentre randomised controlled clinical trial. Arch Dis Child Fetal Neonatal Ed., 2004; 89(5): F394–F398.
14. Ananth CV, et al. Epidemiology of preterm birth and its clinical subtypes. J Matern Fetal Neonatal Med., 2006.
15. David E. Trachtenbarg MD. Care of the premature infant. Am Fam Physician, 1998 May 1; 57(9): 2123-2130.
16. Northway Jr, WH; Rosan, RC; Porter, DY (Feb 16, 1967). "Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia." *The New England Journal of Medicine,* 276(7): 357–68.
17. American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. Pediatrics, 2004; 114(3): 874–877.

18. Saunders RA, Milner AD, Hopkin IE. The effects of CPAP on lung mechanics and lung volumes in the neonate. Biol Neonate, 1976; 29: 178-186.
19. Tagare A, Kadam S, Vaidya U, et al. A pilot study of comparison of BCPAP vs. VCPAP in preterm infants with early onset respiratory distress. J Trop Pediatr, 2010; 56(3): 191–4.
20. Lee KS, Dunn MS, Fenwick M, Shennan AT. A comparison of underwater bubble continuous positive airway pressure with ventilator-derived continuous positive airway pressure in premature neonates ready for extubation. Biol Neonate., 1998; 73(2): 69–75.
21. Morley CJ, Lau R, De Paoli A, et al. Nasal continuous positive airway pressure: does bubbling improve gas exchange? Arch Dis Child Fetal Neonatal Ed., 2005; 90(4): F343–4.
22. Pillow JJ, Hillman N, Moss TJM, et al. Bubble continuous positive airway pressure enhances lung volume and gas exchange in preterm lambs. Am J Respir Crit Care Med., 2007; 176(1): 63–9.
23. Morley CJ, Doyle LW, Brion LP, Hascoet JM, Carlin JB. For COIN Trial investigators. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med., 2008; 358: 700-8.
24. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med., 2010; 362: 1970-9.
25. Makhoul IR, et al. Pneumothorax and nasal continuous airway pressure ventilation in premature neonates. ASAIO J. 2002 Sep-Oct.
26. Lin PW, Stoll BJ: Necrotising enterocolitis, Lancet, 368: 1271-1283, 368.