Original Article

Early versus delayed initiation of nasal continuous positive airway pressure for treatment of respiratory distress syndrome in premature newborns: A randomized clinical trial

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Abstract

Background: This prospective study was performed to identify whether the early use of nasal continuous positive airway pressure (n CPAP) would reduce the rate of endotracheal intubation, mechanical ventilation and surfactant administration.

Materials and Methods: This study was conducted from June 2009 to September 2010 in the Shahid Beheshti University Hospital, Isfahan-Iran. A total of 72 preterm infants with 25-30 weeks gestation who needed respiratory support at 5 min after birth entered the study. Infants were randomly assigned to the very early CPAP (initiated 5 min after birth) or to the late CPAP (initiated 30 min after birth) treatment groups. The primary outcomes were need for intubation and mechanical ventilation during the first 48 h after birth and secondary outcomes were death, pneumothorax, intraventricular hemorrhage, duration of mechanical ventilation and bronchopulmonary dysplasia.

Results: There were no significant differences between the two groups with regard to mortality rate, bronchopulmonary dysplasia and patent ductus arteriosus. The need for surfactant administration was significantly reduced in the early CPAP group ($P = 0.04$). Infants in the early CPAP group less frequently required intubation and mechanical ventilation.

Conclusions: Early n CPAP is more effective than late n CPAP for the treatment of respiratory distress syndrome. In addition, the early use of n CPAP would reduce the need for some invasive procedures such as intubation and mechanical ventilation.

Key Words: Continuous positive airway pressure, premature infant, respiratory distress syndrome

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INTRODUCTION

Neonatal respiratory distress syndrome (RDS) is an important cause of morbidity and mortality in premature infants. The primary cause of neonatal RDS is surfactant deficiency, which leads to decrease in lung compliance and thereby hypoventilation and ventilation perfusion mismatch.[1,2]

In the previous decades, mechanical ventilation was the standard management of RDS in very premature

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infants. However, intubation and mechanical ventilation may be hazardous for the baby. For example, intubation could be traumatic and may increase the risk of airway colonization and infection. Moreover, artificial ventilation might predispose the premature lung to bronchopulmonary dysplasia, which could be prevented by gentle respiratory support during the early hours of life.[3,4]

Continuous positive airway pressure (CPAP) is a positive pressure applied to the airways of spontaneously breathing infants throughout the respiratory cycle and maintains functional residual capacity (FRC) and prevents alveolar collapse at the end of expiration. It has been shown that the application of nasal CPAP (n CPAP) is effective in the post-extubation care of pre-term infants. In addition, n CPAP could decrease the work of breathing and reduce atelectasis by increasing FRC during expiration.[5] On the other hand, some studies have suggested that use of n CPAP during resuscitation of very low birth weigth (VLBW) infants may be beneficial in reducing endotracheal intubation.[6]

In a systematic review, Ho and colleagues assessed the beneficial effects of early n CPAP (the need for $FIO_2 > 0.4$ to maintain oxygen saturation [SPO_2] of more than 85% in the right hand) in the management of RDS. They concluded that n CPAP could be effective in reducing subsequent need for intermittent positive-pressure ventilation (IPPV). But, the majority of their trials were performed before the 1980s, when antenatal steroid use and surfactant administration were not a common practice. Therefore, they suggested re-evaluation of the methods of early CPAP application for management of RDS use in addition to antenatal steroid and surfactant.[2]

The primary objective of this study was to establish whether the very early use of n CPAP has any advantageous over later use in the treatment of RDS in addition to antenatal steroid and surfactant.

MATERIALS AND METHODS

This study was conducted from June 2009 to September 2010 at the Shahid Beheshti University Hospital, Isfahan-Iran. The study was approved by the local research ethics committee and written informed consent was obtained from the parents. Inborn neonates with gestational age between 25 and 30 weeks who received respiratory support because of RDS and an ability to breath spontaneously at 5 min after birth were included. The diagnosis of RDS was based on at least two of the following classic symptoms: need of supplemental oxygen, tachypnea, intercostal retraction, grunting and exclusion of other causes of respiratory distress.

We excluded infants from the study if they had major congenital malformation, demonstrated gasping respiration or required endotracheal intubation due to respiratory failure (a partial pressure of CO_2 more than 60 mmHg and a pH less than 7.25) immediately after birth. Infants were resuscitated according to the Neonatal Resuscitation Program guideline. A T-piece resuscitator (Neopuff Infant Resuscitator; Fisher-Paykel, Auckland, New Zealand) was used in the delivery room for administering CPAP and positive-pressure ventilation.

All pre-term infants included in the study were sequentially numbered and randomized at 1 min after birth to the early CPAP or late CPAP groups using sequentially numbered sealed envelopes and a stratified randomization for gestational age. In the early CPAP group, continuous distending pressure (CDP), at a pressure of 6 cmH_2O, using a nasopharyngeal tube was used in the delivery room. After transporting infants to the NICU, the nasopharyngeal tube was discarded and a binasal prong (equipped with Hudson-prong) was used for delivering CPAP by bubble-CPAP. In the late CPAP group, oxygen was administrated by an oxyhood until 30 min after birth. If the infants required oxygen for more than 30 min, then n CPAP was administered at a pressure of 6 cmH_2O with a single nasopharyngeal tube. After NICU admission, short binasal prongs connected to a bubble-CPAP at the same pressure were used. We administered surfactant (beractant, 100 mg/kg) using the INSURE (Intubation, SURfactant administration, Extubation) method for those newborns who had SPO_2 less than 88% in spite of an FiO_2 more than 0.6, and repeated every 6 h up to four doses if newborns needed FiO_2 more than 0.6 until 48 h after birth. Intubation criteria were arterial pH <7.2, $PaCO_2$ >65 mmHg or recurrent apnea unresponsive to methyl xanthine therapy after initiation of n CPAP.

Brain sonography was done on the 3rd, 7th and 14th days after birth to identify intraventricular hemorrhage (IVH), and newborns who had IVH underwent biweekly skull sonography to detect the possible occurrence of post-hemorrhagic hydrocephalus. The diagnosis of bronchopulmonary dysplasia was based on the need for any supplemental oxygen after 28 days from birth.[7] The diagnosis of sepsis neonatarum was based on the detection of the attending neonatologist.

Primary and secondary outcomes

The primary outcomes were the need for intubation and mechanical ventilation during the first 48 h after birth and the secondary outcomes were death, pneumothorax, intraventricular hemorrhage, need for mechanical ventilation and bronchopulmonary dysplasia.

Statistical analysis

We estimated that a sample size of 36 infants was needed in each group to discover a difference of 33% regarding the need for intubation and mechanical ventilation with 80% power and a significance of 0.05. Student's *t* test, Chi-square test and Fisher's exact *test* were used for continuous and categorical variables, appropriately. Analysis were performed with the SPSS computer program (SPSS Inc., Chicago, IL, USA), with significance accepted for *P*-values <0.05.

RESULTS

A total of 76 infants were enrolled in the study. The study flowchart is shown in Figure 1. The demographic and clinical characteristics of the patients are shown in Table 1.

There were no significant differences between the two groups with regard to birth weight, gestational age, sex, Apgar value at 5 min after birth and frequency of cesarean section.

The overall mortality rate was 19.4%, with 16.7% in the early CPAP group and 22.2% in the late CPAP group (*P* value = 0.7). Sepsis neonatarum was the most common cause of mortality.

Brochopulmonary dysplasia (BPD) occurred in 2.8% of early CPAP group and 5.6% of the late CPAP group (*P* value = 0.5), and these differences were not significant. There was no case of pneumothorax in both groups.

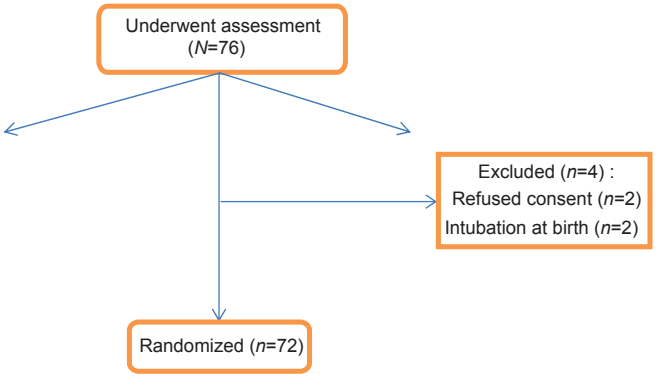

Figure 1: Study flow

Table 1: Baseline demographic and clinical characteristics of the study population

Characteristics	Early n CPAP (*n*=36)	Late n CPAP (*n*=36)	*P*-value
Gestational age (weeks) (mean±SD)	29.06±1.8	29.8±1.7	0.06
Birth weight (g)	983±223.9	1070±184.6	0.08
Male sex (%)	53%	47%	0.64
Apgar score at 5 min	7.39±1.05	7.8±0.7	0.05

The incidence of patent ductus arteriosus was 2.8% in both groups.

The mean duration of hospitalization was 32.3 days for the early CPAP group and 35.9 days for the late CPAP group (*P* value = 0.4).

Overall, more infants in the late CPAP group received surfactant than in the early CPAP group (*P* value = 0.04). In the early CPAP group, 38.9% of the neonates received one dose, 8.3% received two doses and 2.8% received three doses of surfactant. The figures for the late CPAP group were 63%, 8.3% and 5.6%, respectively.

Incidence of IVH was higher in the late CPAP group (83%) than in the early CPAP group (58.3%), and these differences were significant (*P* value = 0.037).

Sepsis occurred about two-times more in the late CPAP group (66.7%) than in the early CPAP group (30.6%), with *P* value = 0.004. Infants in the early CPAP group less frequently required intubation and mechanical ventilation, although it was not statistically significant (*P* value = 0.06).

DISCUSSION

In the present study, we found that the introduction of early n CPAP for management of RDS can reduces the need for endotracheal intubation and surfactant administration in pre-term infants. Moreover, early use of n CPAP have been associated with a lower incidence of sepsis and IVH.

Application of CPAP could increase tidal volume and FRC. At histological examination, surfactant-deficient lungs have areas of atelectasis and overinflation, which could be effectively prevented by application of n CPAP shortly after birth.[8-10] Therefore, early application of n CPAP may be effective in the management of RDS. Previous descriptions have been described in trials in which "early" CPAP was started at a variable period of time extending several hours after birth. However, the best time for starting n CPAP has never been determined for premature infants by randomized controlled trials.[2,11-14]

Krouskop and coworkers compared two methods of n CPAP application in pre-term infants: early CPAP (FiO_2 requirement more than 0.4) and late CPAP (FiO_2 requirement more than 0.7) for treatment of RDS. They did not find any differences in survival or complications between the groups. However, the mean birth weight of their study groups was more than 1700 g, which is more than our patients' weight.[11]

Han and colleagues randomly allocated 82 pre-term infants to the early CPAP group (n CPAP at birth) or the late CPAP group (when FiO_2 reached more than 0.5). They found no differences in outcome with regard to death or intubation and mechanical ventilation.[8] Surfactant was not administered in this study and one explanation for the lack of early CPAP efficacy is that patients may not be given great benefit from CPAP use without surfactant therapy.

Sandri and colleagues evaluated the benefits of prophylactic n CPAP in infants of 28–31 weeks gestation. They randomly allocated 230 infants to prophylactic (started within 30 min of birth, irrespective of oxygen requirement) or rescue (when FiO_2 requirement more than 0.4) n CPAP. They concluded that prophylactic n CPAP could not reduce the need for mechanical ventilation or surfactant administration.[12] In contrary to our study, they started n CPAP within 30 min after birth and not in the delivery room. Therefore, the surfactant-deficient lungs of their patients might be atelectatic before n CPAP use.

In a retrospective study, Gittermann and coworkers found that the early use of n CPAP (applied very soon after initiation of respiratory distress) could significantly reduce the need for intubation and mechanical ventilation without decreasing the incidence of bronchopulmonary dysplasia,[13] which is comparable to our results.

Miksch *et al*. performed a retrospective study to assess the beneficial effects of early n CPAP for treatment of RDS in very low birth weight infants. They found that in infants with birth weight less than 1000 g, the use of early n CPAP significantly reduced intubation rate, duration of ventilation and incidence of bronchopulmonary dysplasia.[10]

Morley and colleagues randomized 610 infants with a gestational age of 25–28 weeks to CPAP or intubation an ventilation at 5 min after birth, they found no significant differences in bronchopulmonary dysplasia and death between the groups.[4]

De Klerk and colleagues showed that early application of n CPAP (usually during 10 min of admission) could decrease endotracheal intubation, surfactant administration and duration of mechanical ventilation, which is corresponding to our results.[14]

In our study, surfactant administration was reduced in the early CPAP group. Therefore, we found that the early use of n CPAP could be cost-effective in the treatment of RDS, which is comparable to the study of Miksch *et al*.[10]

This study has some limitations, including the small number of study groups and absence of long-term outcomes. Also, it was not blinded. However, it has a unique concept because of very early use of n CPAP in the delivery room.

In conclusion, our study demonstrated that early use of n CPAP is an effective and safe method for the treatment of RDS in pre-term newborns. Moreover, early CPAP could reduce the need for some invasive procedures such as intubation and mechanical ventilation.

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