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Comparison of the Effectiveness of Continuous Positive Airway Pressure (CPAP) Therapy with a Combination of High-Frequency Oscillations and CPAP in the Treatment of Respiratory Distress Syndrome in Infants

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ABSTRACT

Background: Invasive mechanical ventilation in infants suffering from respiratory distress syndrome (RDS) is associated with some complications, such as chronic lung disease, and therefore, the tendency to use non-invasive methods is increasing. The present study aimed to compare the effect of non-invasive continuous positive airway pressure (CPAP) and a combination of high-frequency oscillation ventilation (HFOV) and CPAP in the treatment of RDS in infants.

Methods*:* In this clinical trial, 37 infants suffering from RDS admitted to the Neonatal Intensive Care Unit of Hajar Hospital in Shahrekord were randomly assigned to two groups treated with CPAP alone and CPAP plus HFOV. The baseline information, including gestational age, time of birth, weight, gender, duration of hospitalization, duration of oxygenation and CPAP, the time of transition to oral feeding, and hemodynamic parameters, were recorded. The obtained data were analyzed in Stata software.

Results: The mean scores of the length of hospitalization, the time to start and complete oral feeding, as well as the duration of CPAP and oxygenation, were higher in the CPAP group, as compared to those in the HPA+CPAP group; nonetheless, the differences were significant only for the duration of oxygenation ($P<0.05$).

Conclusion: As evidenced by the obtained results, the use of HFOV+CPAP led to a more significant reduction in the duration of oxygen therapy, as compared to CPAP, in preterm neonates suffering from RDS.

Keywords: Continuous positive airway pressure, High-frequency oscillation ventilation, Respiratory distress syndrome

Introduction

Respiratory distress syndrome (RDS) is a life-threatening pulmonary disorder and one of the common causes of mortality and morbidity in preterm neonates (1). The RDS is a type of pulmonary defect commonly observed in preterm labor caused by extensive microatelectasis resulting from a lack of surfactant leading, loss of functional residual capacity (FRC), and disrupted ventilation/perfusion ratio (2, 3). This condition is followed by some consequences, including the weakness of respiratory muscles and decreased pulmonary compliance which leads to a decrease in oxygenation, cyanosis, and respiratory and metabolic acidosis, accompanied by hypoxemia due to elevated pulmonary vascular resistance , as well as the right-to-left shunt via the ductus arteriosus (3, 4).

In recent decades, numerous studies have been performed on new therapies for neonates suffering from RDS, including the administration of

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antenatal steroids to mothers, exogenous surfactants to newborns, and modern ventilation techniques (4). And the use of some supportive methods and treatments in premature infants, such as the use of kangaroo care even in infants under ventilator, trophic and early feeding in premature infants, and trancotaneous feeding(5, 6). Despite the improvements in infants' survival using the mentioned therapeutic methods, RDS complications, such as chronic pulmonary disease, have remained significant.

Moreover, it is not clear that such complications are the result of the disease or a consequence of treatment complications (7). Although new methods of mechanical ventilation and other medical treatments raised high expectations, the incidence of complications has not decreased, and mechanical ventilation has remained a serious risk factor for chronic lung disease and bronchopulmonary dysplasia (8).

Today, researchers have focused on less invasive ventilation methods, such as continuous positive airway pressure (CPAP) and high-frequency oscillation ventilation (HFVO) to improve oxygenation and reduce disease complications. Studies have indicated that early use of surfactants with CPAP reduces the need for mechanical ventilation, as well as the prevalence of air leak syndrome and chronic lung illnesses (2, 8-11). Nonetheless, in a randomized controlled trial, 33%-83% of the patients under CPAP needed mechanical ventilation during the course of treatment, and some of them did not respond to CPAP since it did not necessarily improve alveolar ventilation or CO2 removal (10, 12).

In this regard, recent studies have pointed out that non-invasive ventilation techniques that actively support gas exchange can be more effective (11, 13). The HFOV is a non-invasive ventilation method in which a small current volume is given to the neonate through ventilation at very high speed (more than 150 minutes), resulting in a lower risk of lung injury(14) (12).

In the present study, the researcher aimed to reduce the effect of the high-frequency breathing method, which is more suitable for neonates due to pulmonary acceptance resulting from lower current volume. Moreover, according to previous studies, it probably reduces the incidence of some complications by continuous positive pressure breathing method. The present study aimed to compare the effects of CPAP and CPAP+HFVO, two non-invasive ventilation methods, on the treatment of neonates with RDS.

Methods

Study population

This double-blind clinical trial (IRCT 20180915041040N3) was conducted on 40 neonates aged less than 35 weeks who suffered from RDS and were admitted to the neonatal intensive care unit of Hajar Hospital in Shahrekord, Iran. The sample size was calculated based on a study that reported mortality in patients treated with HFO and normal aeration as 0.32 and 0.52, respectively(15, 18). The sample size was estimated at 40 cases in the form of two groups (n=20 in each group) who were selected by the simple random allocation method.

P = Q = 0.5, Alpha = 0.05, d = 0.23, N = ((Z2 * P * Q) / D2) = 18 P = Q = 0.5, Alpha = 0.05, d = 0.23, N = ((Z2 * P * Q) / D2) = 18

Three infants needed mechanical ventilation and were ruled out from the study due to respiratory failure, pulmonary hemorrhage, and sepsis. The disease was diagnosed based on clinical symptoms, changes in arterial blood gas, and changes in chest X-rays. The exclusion criteria were as follows: death of infants during the study, chromosomal anomalies, associated severe anomalies, pulmonary diseases other than RDS, congenital heart disease, intraventricular hemorrhage (IVH) Grade 2 and above, and parents' unwillingness to participate in the study. The study was approved by the Ethics Committee of Shahrekord University of Medical Sciences (REC.SKUMS.IR29101395).

Study interventions

After obtaining written consent from the legal guardians, the infants were randomly assigned to two groups using a computerized random number table according to the last figure of the number of their medical files as CPAP group and CPAP+HFVO group. In both groups, two-way nasal mask or prong was used, and the CPAP+HFVO-treated group underwent HFOV for 2 h with a mean airway pressure (MAP) equivalent to the Ppositive end-expiratory pressure (PEEP) applied by the CPAP at a frequency of 10 Hz and a degree of oscillation so that the shaking was observed at the anterior neck and chest.

Fraction of inspired oxygen (FIO2) was determined based on the need of the infant so that oxygen saturation was preserved between 90% and 95%, and after 2 h, the infant was connected to the CPAP with the same settings as the first group. Infants in group 1 under CPAP were treated with PEEP 6-8 and FIO2 40% using the

Stephan ventilator(Sophie). If the FIO2 over 40% is needed to maintain infants' oxygen saturation between 90% and 95%, the surfactant should be administered intratracheally.

Ventilator settings (FIO2, MAP, oscillation amplitude, and frequency), and infants' hemodynamic parameters, including heart rate, respiratory rate, and arterial oxygen saturation, were monitored in the first two hours every 30 min and then every one hour until separation from CPAP. In addition, 1 h after connection to CPAP or HFOV, the chest X-ray was taken to check air-trapping. In both groups, arterial blood gas analysis was performed before and two hours after ventilator connection.

Statistical analysis

The results were presented as mean±standard deviation for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. The normality of data was analyzed using the Kolmogorov-Smirnoff test. Categorical variables were compared using the chi-square test or Fisher's exact test when more than 20% of cells with an expected count of less than 5 were observed. Quantitative variables were also compared with t-test or Mann U test. The data were analyzed in SPSS software (version 16.0). A p-value of 0.05 or less was considered statistically significant.

Results

As evidenced by the results of this study, out of 37 children suffering from RDS, 20 cases (17 boys and 3 girls) were treated with CPAP alone, while 17 subjects (9 boys and 8 girls) received CPAP and HFOV. Statistical analysis pointed to a significant difference between the two groups in terms of gender distribution(P=0.038). Moreover, the comparison of groups in terms of gestational age and birth weight illustrated that there was no significant difference between the groups (Table 1). There was no significant difference between the two groups in terms of length of hospitalization, the time of onset and completion of oral feeding, and CPAP duration (P>0.05). Nonetheless, the mean duration of oxygenation was significantly shorter in combination therapy (P=0.036; Table 2).

The overall complication rate after treatments was similar in the groups scheduling for CPAP alone and CPAP+HFOV. In this regard, in the combination therapy group, one neonate suffered from apnea and another one had pulmonary hemorrhage, while one infant died during hospitalization, indicating a mortality rate of 5.9%. In the CPAP group, in-hospital death occurred in two infants with a mortality rate of 10.0%, whereas intracranial hemorrhage and apnea occurred in one and three infants, respectively. In general, the two groups did not differ in post-treatment outcomes (P>0.05; Table 3)

Table 1. Between-group comparisons regarding participants' characteristics

Characteristics			Group		P-value
			HFOV+CPAP	CPAP	
Gender	male	N (%)	9(52.9)	17(85)	0.038
	Female	N (%)	8(47.1)	3(15)	
Gestational age	Mean ± S.D		34.17±1.18	32.95±2.23	0.05
Birth weight (gram)	Mean ± S.D		2164.7±471.39	2103.5 ±538.73	0.718

Table 2. Between-group comparisons regarding the duration of hospitalization, the time of onset and completion of oral feeding, duration of oxygen therapy, and CPAP duration of participants

variable	Group		P-value
	HFOV+CPAP Mean ± S.D	CPAP Mean ± S.D	
Duration of hospitalization(4)	8.68±315	13.05±9.88	0.09
Start time of oral feeding (4)	3.87±2.72	8.05±10.30	0.126
Full oral feeding time (4)	8.12±3.32	12.72±10.50	0.104
Duration of need oxygen	63.20±42.20	184.43±225.15	0.036
CPAP Duration (hour)	38.47±35.88	58.64±42.32	0.131

Table 3. Prevalence of complications between the groups

variable	Group		P-value
	HFOV+CPAP N (%)	CPAP N (%)	
Apnea	1 (5.8)	3 (15.0)	0.367
Intracranial hemorrhage	0 (0.0)	1 (5.0)	0.541
Pulmonary hemorrhage	1 (5.8)	0 (0.0)	0.459
Chronic lung disease	0 (0.0)	0 (0.0)	1.000
Death	1 (5.8)	2 (10.0)	0.562

Discussion

The present study aimed to compare the effect of nasal CPAP and HFOV +CPAP on the treatment of newborns with RDS. It was observed that the length of hospital stay, the time of start and completion of oral feeding, time of oxygenation therapy, and duration of CPAP in the HFOV+CPAP group were less than those in the CPAP group; however, the difference was statistically significant only with respect to the duration of oxygen therapy. Furthermore, there was no significant difference in the prevalence of apnea, necrotizing enterocolitis, pneumothorax, pulmonary hemorrhage, intracranial hemorrhage, and in-hospital death between the two groups.

The effectiveness of HFOV has been assessed and compared with other ventilation methods in some other studies which yielded contradictory results. In their meta-analysis, Sud et al. (2016) compared the use of HFOV and conventional mechanical ventilation in the treatment of children and adults with RDS. In eight trials on 1,779 participants, HFOV did not reduce the risk of in-hospital death. The ability of the lungs to oxygenate the blood, which was measured after randomization within 24 to 72 hours of ventilation, was improved by 18%-26% in subjects who received HFOV.

The HFOV did not exert any effect on the reduction of the time required for mechanical ventilation. The risk of adverse effects, including hypotension or secondary damage to the lung due to high airway pressure, was not increased (13, 16). In agreement with the findings of the study by Sud et al., the present research revealed no significant effect on HFOV-related mortality and complications; nonetheless, unlike their study, the duration of mechanical ventilation decreased. This discrepancy in the results of these studies can be ascribed to the comparison of HFOV and mechanical ventilation in the stated study, and the comparison of HFOV and CPAP in the present research.

In another study comparing the outcome of non-invasive positive pressure ventilation (PPV) and HFOV, it was observed that HFOV was more effective in the elimination of carbon dioxide from the lung, compared to non-invasive PPV (6, 7). In a study to compare two non-invasive ventilation methods of HFOV and CPAP in premature neonates with moderate and severe delayed respiratory syndrome, the need for invasive mechanical ventilation was significantly lower in the HFOV group, as compared to that in the CPAP group (23.44% vs. 56.4%). In addition, similar to the present study, the prevalence of intra-ventricular hemorrhage and bronchopulmonary dysplasia was similar in the two groups, and the mortality rate was not significantly different between the two groups (12, 14).

In another study which compared the effectiveness of HFOV and CPAP in newborn infants with transient neonatal tachypnea, the duration of tachypnea in the HFOV group was found to be half of that in the CPAP group. In the HFOV group, the duration and rate of oxygenation were both significantly lower when compared to the CPAP group. No adverse event was observed in any of the groups, and the HFOV was well tolerated (14, 17). Similar results were obtained in the present study for infants with RDS.

The HFOV is non-current ventilation delivered at a very high speed, and the volume of delivered gas is less than the anatomical dead volume. The basis of this phenomenon is that blowing a small amount of gas at a high speed causes less alveolar pressure and less likelihood of injury (15, 18). The HFOV reduces the injury caused by pressure due to its compatibility with the neonatal lung membrane (16, 19).

Studies have pointed out that infants treated with HFOV have higher mean air pressure, as compared to those who undergo common mechanical ventilation methods. In addition, a faster increase (less than 16 hours) in relative arterial oxygen pressure (PaO2) was observed in infants under HFOV, in comparison with those under mechanical ventilation. Furthermore, the mortality rate for HFOV and conventional ventilation during 30 days was 32% and 52%, respectively, pointing to a significant difference. All of these results confirm the safety and efficacy of HFOV, compared to mechanical ventilation (17, 20).

Nevertheless, there is less evidence for the effectiveness of HFOV, compared to CPAP, and the results of studies have demonstrated that the use of HFOV in children undergoing CPAP led to a significant reduction in PCO2 and a marked increase in pH (11). Moreover, in comparison with CPAP, HFOV causes a more noticeable reduction in the need for mechanical ventilation; nonetheless, it does not significantly affect the incidence of complications and mortality rates (12, 14).

In the present study, the effectiveness of simultaneous use of HFOV and CPAP was observed, in comparison with CPAP alone. The use of HFOV decreased the duration of oxygen therapy with no significant adverse events and disease-related death. However, it is recommended that subsequent studies use a larger sample size to

further investigate these results.

Conclusion

In the present study, the use of a concomitant of HFOV and CPAP reduced the duration of oxygen therapy. Furthermore, there was no significant difference between the two groups in the prevalence of complication and death.

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Conflicts of interest

None.

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