Predictors of Nasal Continuous Positive Airway Pressure Failure in Preterm Infants With Respiratory Distress Syndrome

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Received: 12 May 2023; Accepted: 24 Dec. 2023

Abstract- Respiratory support in infants with respiratory distress syndrome (RDS) plays an important role in the reduction of mortality and complications, but the treatment fails in some infants. This study aimed to identify the predictors of continuous positive airway pressure (CPAP) failure in preterm infants with RDS. This cross-sectional retrospective study was conducted on RDS-diagnosed preterm infants admitted to the neonatal intensive care unit of Fatemieh Hospital (Hamadan city) in 2021-2022. The infants were examined in terms of risk factors for CPAP failure. Data extracted from the medical records were recorded in a checklist and analyzed with SPSS version 21 software at a confidence level of 95%. CPAP failure was recorded in 37.6% of the studied 202 infants. The need for resuscitation at birth, low gestational age, low birth weight, multiple births, low 1-min and 5-min Apgar scores, the need for higher FIO2 and PEEP, acidosis, and the need for surfactant administration were significantly associated with CPAP failure. In logistic regression, low gestational age (OR 1.30, 95% CI: 1.082-1.576) and the need for resuscitation at birth (OR 0.426, 95% CI: 0.202-0.898) were the major predictors of CPAP failure. Lower gestational age and the need for PPV in the delivery room are good predictors of CPAP failure in preterm infants with RDS, who receive nasal CPAP as primary respiratory support.

Acta Med Iran 2024;62(Janyary-February):35-39.

Keywords: Preterm infants; Respiratory distress syndrom; Continuous positive airway pressure

Introduction

Despite recent advances in the care of preterm infants, respiratory distress syndrome (RDS) is still a major cause of death in preterm infants, and continuous positive airway pressure (CPAP) is a simple, noninvasive, and cost-effective treatment for RDS that reduces the need for mechanical ventilation and the risk of mortality and bronchopulmonary dysplasia (BPD) (1). Large clinical trials have proved that CPAP immediately after birth, without intubation for surfactant therapy, is associated with better respiratory outcomes than a predominantly intubated group (2,3). However, 20-40% of CPAP infants are associated with failure and require intubation and mechanical ventilation. The consequences of CPAP failure include a significant increase in the risk of death, intraventricular hemorrhage, and BPD (3).

In general, CPAP failure predictors can be classified into (1) baseline features such as low gestational age, low birth weight, and the need for positive pressure ventilation at birth, (2) severity of respiratory distress, including high respiratory distress scores, chest radiographic findings, the need for $FiO_2 \geq 30$ in the first hours of life, the need for surfactant and blood gas parameters, and (3) management issues, including delay in the CPAP start, delay in surfactant administration, and skills and experiences of the personnel of the neonatal department in using CPAP (4-8). The identification of the risk factors of CPAP failure increases the experience of treatment personnel in CPAP management, on the one hand, and allows for the selective use of mechanical ventilation, on the other hand, thereby lowering the risk

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of complications and saving the infant. Therefore, this study was designed and implemented to identify the predictors of nasal CPAP failure in premature infants with RDS.

Materials and Methods

This cross-sectional descriptive/analytical study was carried out on all RDS-diagnosed infants requiring CPAP treatment hospitalized in the neonatal intensive care unit of Fatemieh teaching-treatment center (Hamadan city) in 2019-2019. All infants with a gestational age of <37 weeks and moderate respiratory distress (score=7) undergoing CPAP treatment were included in the study. Infants with intubation immediately after birth, 5-min Apgar score ≤3, chromosomal abnormalities or multiple congenital malformations, congenital lung diseases, and those with apnea and septic shock were excluded from this research.

For all eligible infants, nasal CPAP with initial positive end-expiratory pressure (PEEP) of 5-7 cm H_2O and FiO_2 was set to maintain SpO_2 between 88 and 93%. Based on radiological findings, surfactant was prescribed by the InSurE (Intubate Surfactant Extubate) method for an infant with RDS who needed an FiO_2 of >0.30. Intubation and mechanical ventilation were applied in the case of at least one of the following conditions with maximum CPAP settings: (a) exacerbation of respiratory distress, (b) oxygen saturation ≤87% and/or PaO_2 ≤50 mmHg, c) pH <7.2 with $PaCO_2$ ≥55 mm Hg or base excess of blood (BE) >-15, (d) recurrent apneas (≥3 episodes/h) or apnea of any severity requiring positive pressure ventilation, and (e) signs of systemic shock requiring inotropic support (dopamine or dobutamine >15 μg/kg/min).

"CPAP failure" was defined as the need for mechanical ventilation in the first 72 h after birth following maximum PEEP=7 cm H_2O and maximum FiO_2 ≥0.60 (9).

"The success of CPAP" was defined as continued CPAP, improved respiratory distress, SpO_2 >90% with FiO_2 <25%, and PEEP <4 cm H_2O.

The data collection tool was a researcher-made checklist according to the objectives and variables of the study to extract the required data from the medical records at the hospital. Birth weight, gestational age, infant gender, route of delivery, parity, resuscitation at birth, 1-min and 5-min Apgar, maternal diseases, blood gas analysis, surfactant administration, and intubation were the variables extracted from the patients' medical records. The effects of these variables were evaluated on the failure and success of CPAP and hospitalization consequences.

The obtained data were analyzed at descriptive and inferential levels using SPSS version 21 software. The frequencies of response and non-response to CPAP treatment were compared by Chi-square and Fisher's exact tests for qualitative variables, and Student's t-test and Mann-Whitney test were used for quantitative variables. P<0.05 were considered the statistical significance level.

Results

In this study, 76 (37.6%) out of 202 infants did not respond to CPAP treatment (CPAP failure). Male gender, maternal disease, and receiving antenatal steroids were not associated with CPAP failure, but the need for resuscitation at birth, lower gestational age, low birth weight, multiple births, and low 1-min and 5-min Apgar scores were significantly associated with CPAP failure (Table 1).

In blood gas analysis, CPAP failure was significantly correlated with severe acidosis (pH <7.2) and PCO_2 >65 in infants with RDS (Table 2).

Of 160 and 42 babies who needed and did not need surfactant administration, 66 (41.2%) and 10 (23.8%) infants did not respond to CPAP treatment, respectively (P=0.038). The need for higher FIO_2 and PEEP was also significantly associated with CPAP failure (Table 3).

In logistic regression, lower gestational age (OR 1.30, 95% CI: 1.082-1.576) and the need for resuscitation at birth (OR 0.426, 95% CI: 0.202-0.898) were the most important predictors of early CPAP failure (Table 4).

Table 1. Comparison of characteristics between CPAP failure and CPAP success infants

Variables	CPAP success	CPAP failure	*P*
Male sex; n (%)	60(62.5)	36(37.5)	0.972
Gestational age (weeks)	32.34±2.78	30.78±2.91	0.003
Birth weight (g)	1829.44±523.31	1588.61±502.82	0.002
Multiple birth; n (%)			
Singleton	100(65.8)	52(34.2)	0.028
Twins &Triplets	22(47.8)	24(52.2)	
Cesarean section; n (%)	96(60.8)	62(39.2)	0.622
1 min APGAR	7.18±1.43	5.71±1.79	<0.001
5 min APGAR	8.73±1.01	7.42±1.80	<0.001
Need for resuscitation at birth	22(45.8)	26(54.2)	0.004
Maternal disease*	44(66.7)	24(35.3)	0.626
Antenatal steroids (%)	28(73.7)	10(26.3)	0.110
Mortality, n (%)	0(0)	38(50.0)	<0.001
NICU stay (days)	17.68±13.76	15.00±11.58	0.157

*PROM, Diabetes, Preeclampsia,

Table 2. Comparison of ABG analysis between CPAP failure and CPAP success infants

Variables		CPAP success	CPAP failure	*P*
SPO2	**>88%**	74(63.8)	42(36.2)	0.244
	≤88%	34(54.8)	28(45.2)	
PH	**<7.2**	12(33.3)	24(66.7)	<0.001
	≥7.2	96(67.6)	46(33.4)	
PCO2	**<65**	108(62.8)	64(37.2)	0.003
	≥65	0(0)	6(100)	
PO2	**>50**	86(58.9)	60(41.1)	0.302
	≤50	22(68.8)	10(31.2)	

Tabe 3. Comparison of characteristics between CPAP failure and CPAP success infants

Variables	CPAP success	CPAP failure	*P*
Age of starting CPAP (min)	59.46±36.98	45.35±55.31	0.105
Age at surfactant administration (min)	129.10±61.63	125.10±68.75	0.688
Max FIO_2	43.6±4.96	46.84±8.36	0.005
SPO_2/FIO_2	2.0±2.51	1.0±8357	0.025
Max PEEP	4.96±0.37	5.10±0.51	0.024

Table 4. Predictors of CPAP failure: Logistic regression model

Predictors	Odds ratio	95% CI	*P*
Birth weight	1.00	0.999-1.001	0.663
Gestational age	1.30	1.082-1.576	0.005
Multiple birth	0.537	0.256-1.127	0.100
Required PPV in delivery room	0.426	0.202-0.898	0.025

Discussion

A CPAP failure rate of 37.6% was obtained in the present study. This value is in the range of those reported in previous studies (between 22.1 and 61%), namely 14.7% (Murki *et al*.,) (9), 49% (Dobryanskyy *et al*., (10), 61% (Radicioni *et al*.,) (11), 50% (Kakkilaya *et al*.,) (12), 22.1% (Sunil *et al*.,) (13), and 43% (Dargaville *et al*.,) (3). This difference in failure rates among studies may be attributed to differences in sample size, gestational age, inclusion criteria, definitions of failure, and standard care practices.

In many previous studies, predictors of CPAP failure were lower gestational age, lower birth weight, lack of steroids, parity, more severe RDS, presence of PDA, sepsis/pneumonia, higher FiO_2 requirement, and continuous respiratory distress after stabilization on CPAP (9).

Steroid administration to pregnant women at risk of preterm delivery accelerates fetal lung maturation, but it was not significantly related to CPAP failure in our study, which corresponds to the results of Pillai *et al.,* (5) and Arora *et al*., (14). Moreover, the response to CPAP was not affected by other maternal diseases, such as diabetes mellitus and hypertension, which is in line with the results of Sabry *et al*., (15). These factors seem to be responsible for preterm birth, the effects of which need confirmation by a larger scale study.

Surfactant treatment is another highly well-known factor that helps in lung maturation and, consequently, in RDS treatment. Our study was not related to CPAP failure, which is consistent with the study by Sabry *et al*., (15). Although the role of surfactant is undeniable, the outcome seems to depend on multiple factors not a single factor. Additionally, the surfactant administration time in our study did not influence the response to CPAP. However, Murki *et al*., (9) and Dobryanskyy *et al*., (10) reported that earlier initiation of surfactant in preterm infants by a less invasive method was significantly associated with a decrease in CPAP failure.

Paying attention to oxygenation, CPAP settings, and acid-base balance is of paramount importance because our study revealed that the need for high FiO_2 was a significant variable affecting early CPAP failure, which agrees with the study by Murki *et al*., (9). Sabry *et al.,* (15), however, found that the response to CPAP was not related to the need for FiO_2, but it was associated with an increase in FiO_2 during 2 h after the start of CPAP. Radicioni *et al*., (11) observed a significant relationship between the SPO_2-to-FiO_2 (SF) ratio and CPAP failure. Kakkilaya *et al*., (12) and Pillai *et al*., (5) presented evidence that the need for FiO_2> 0.3 was a predictor of CPAP failure. Studies generally suggest that infants with CPAP failure needed more initial Flow rate, FiO_2, and PEEP. Significant acidosis values were obtained in the failure group compared to the successful group in our study and Sabry *et al*., (15).

Similar to a study by Afjeh *et al*., (16), our study showed that the Apgar score was a predictor of CPAP failure in infants with very low birth weight and RDS. On the contrary, Permatahati (17) reported that the Apgar score was not a significant predictor of nasal CPAP failure.

Our study showed that lower gestational age and the need for resuscitation in the delivery room were the main factors of CPAP failure, which is in line with some other studies (5,17). In our investigation, the average gestational age was lower in the CPAP failure group, which corresponds to Sabry *et al*., (15), but it disagrees with Dell'Orto *et al*., (18). It can also be concluded that more preterm infants need more in-room resuscitation in the delivery room along with higher severity of RDS, which affect CPAP failure (15).

In our study, deaths occurred in half of the infants with RDS who did not respond to CPAP treatment, and their mortality rate was significantly higher than that of infants who responded to CPAP. Similar to our findings, CPAP failure was significantly associated with high infant mortality rates in studies by Dargaville *et al*., (2), Ammari *et al*., (7), and Sahussarungsi *et al*., (19). Murki *et al*., (9) noticed a significantly higher frequency of comorbidity and length of hospitalization in infants with CPAP failure.

The recently introduced concept of the "golden hour" in neonatal medicine highlights the critical importance of caring for infants in the first 60 min of life after birth; the first few hours to days are also vital (20). This delay in starting CPAP may be the reason for the worsened blood gas parameters after 2 h and the increased failure rate, highlighting the need for early administration of CPAP.

The limitations of our study include its retrospective nature and no records of long-term complications of prematurity, such as retinopathy of prematurity, necrotizing enterocolitis, and BPD.

Lower gestational age and the need for PPV in the delivery room are good predictors of CPAP failure in preterm infants with RDS, who receive nasal CPAP as primary respiratory support.

Acknowledgments

This article has been extracted from Dr. Rozhin Hesami dissertation for obtaining a doctorate in general physician. The authors express their appreciation to NICU staff and the Vice-chancellor of Research and Technology of Hamadan University of Medical Sciences.

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