Predictor Factors of Continuous Positive Airway Pressure Failure in Preterm Infants with Respiratory Distress

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Abstract

Respiratory distress contributes significantly to mortality, and morbidity in preterm infants. The incidence of nasal continuous positive airway pressure (CPAP) failure is remarkably high. There are limited data available regarding nasal CPAP failure in Indonesia, and this study is expected to be a reference in taking preventive measures to reduce mortality and morbidity in preterm infants. To determine predictive factors of nasal CPAP failure in preterm infants with respiratory distress. A retrospective cohort study was conducted in preterm infants with respiratory distress at the Neonatology ward of Dr. Sardjito Hospital during January 2017-July 2019. Chi-square or Fisher's exact tests, followed by multivariate logistic regression analysis with backward method, was used to identify factors contributing to nasal CPAP failure. A total of 150 infants were included in this study. Fifty-three (37.8%) infants had nasal CPAP failure. Bivariate analysis showed birth weight $<1000\,g$, singleton, APGAR score 4-7, premature rupture of membrane (PROM), Downes score, and initiation of fractional concentration of inspired (FiO_2) requirement were all risk factors of nasal CPAP failure. However, only birth weight $<1000\,g$ ($P=.022$; OR 2.69; CI 95% 1.34-5.44), initial Downes score ($P=.035$; OR 2.68; CI 95% 3.10-24.11), and initiation of FiO_2 requirement $\geq30\%$ ($P=.0001$; OR 3.03; CI 95% 2.04-4.50) were significant predictors for nasal CPAP failure by multivariate analysis. Birth weight $<1000\,g$, singleton, initial Downes score, and initiation of FiO_2 requirement $>30\%$ were significant predictors of nasal CPAP failure in preterm infants with respiratory distress.

Keywords

preterm infants, CPAP, respiratory distress

Received February 11, 2021. Received revised March 26, 2021. Accepted for publication March 10, 2021.

Introduction

Respiratory distress contributes significantly to mortality, and morbidity in preterm infants, and is the most frequent cause of neonatal intensive care unit (NICU) admission. Continuous positive airway pressure (CPAP) has been known to reduce breathing effort, oxygen demand, periods of apnea, risks of reintubation in infants from mechanical ventilation, length of stay, referrals to tertiary hospital, in addition maintaining functional residual capacity, and to prevent lung and upper airway collapse. Several studies have suggested that CPAP failure is associated with higher risk of mortality and adverse outcomes including pneumothorax, bronchopulmonary dysplasia, and intraventricular hemorrhage.[1,2] Previous studies that evaluated gestational age, Downes score, antenatal steroid, patent ductus arteriosus (PDA) and initial FiO2 requirement have provided varying results. Study by Koti et al,[3] reported that no or partial exposure to antenatal steroid, whiteout on the chest X-ray, PDA, sepsis/pneumonia and Downes score >7 or $FiO_2 \geq50\%$ after 15 to 20 minutes of CPAP might predict CPAP failure. This study aimed

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to determine predictive factors of nasal CPAP failure in preterm infants with respiratory distress.

Methods

Study Population

This study was conducted at the level II and III Neonatal care unit of Dr. Sardjito Hospital Yogyakarta Indonesia. All consecutively born preterm infants with gestation <37 weeks and were admitted to Neonatal care unit with CPAP as primary respiratory support due to respiratory distress were included. Referral cases, medical records with incomplete variable data and major congenital malformation with orofacial involvement were the exclusion criteria.

Study Design

This was a retrospective cohort study conducted during January 2017-July 2019. The respiratory support for all infants managed initially on nasal CPAP was defined from the medical record. The infants with respiratory distress were diagnosed to have failed nasal CPAP with one of the criteria setting PEEP >8, FiO_2 >40%, required a mechanical ventilation or intubation before 72 hours of life. Nasal CPAP was considered to be successful if infants with respiratory distress underwent nasal CPAP setting PEEP 5-8, FiO_2 21%-40%. Data collection of maternal variables included multiple births, pregnancy-induced hypertension, PROM, cesarean section and antenatal steroids. Gestational age was calculated based on Dubowitz score or Ballard score. The evaluated infant variables evaluated included birth weight and gestational age, APGAR scores at one-minute minutes, delivery room management (oxygen, positive pressure ventilation via bag and mask), initial FiO_2 requirement after 15 to 20 minutes of CPAP, positive end expiratory pressure (PEEP), and initial Downes score after resuscitation. The other clinical data recorded were clinical results and echocardiography proven for congenital heart disease (CHD. Birthweight was measured by the smallest unit of 10 g less than 1 hour of age. Full doses of dexamethasone antenatal steroids as administration 4 times intravenously. APGAR scores were assessed in the first minute of neonatal resuscitation. The initial Downes score were assessed prior to nasal CPAP. Meanwhiles initial FiO_2 requirement was based on FiO_2 levels 15 to 20 minutes after nasal CPAP was installed. Neonatal hypothermia is defined as an abnormal thermal state in which the newborn's body temperature drops below 36.5°C (97.7°F). Hypoglycemia as a plasma glucose level of less than 30 mg/dL

(1.65 mmol/L) in the first 24 hours of life and less than 45 mg/dL (2.5 mmol/L). Prolonged PROM was determined more than 18 hours between the rupture and the onset of labor. Neonatal sepsis was defined as bacteremia occurring at ≤72 hours, which met 4 of following criteria temperature instability criteria, central nervous system dysfunction, respiratory distress, cardiovascular disturbance, gastrointestinal symptom, renal insufficiency, and hematology disorder. Small for gestational age (SGA) was a birth weight below the 10th percentile, while percentile between the 10th and 90th was categorized into appropriate for gestational age (AGA) and >90th percentile was considered large for gestational age (LGA) based on local Yogyakarta, Indonesian curves.[4]

Ethical Approval

The study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Universitas Gadjah Mada/Dr. Sardjito Hospital Yogyakarta, Indonesia number KE/FK/0882/EC July 31 2019.

Statistical Analysis

Baseline characteristic predictors and outcome variables were compared between infants who had successful and failed nasal CPAP. Comparable categorical data between the 2 groups were analyzed using the Chi-square test or Fischer's exact test when appropriate. A *P*-value less than .05 was considered significant. For multivariate analysis, logistic regression models were used to investigate the effects of clinical indices of respiratory function coupled with potential demographic predictors. The statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 22 (IBM Corp., Chicago).

Results

Subjects of Study

We enrolled 150 neonates in the study with the proportion of male and female was 1.1:1. The median gestation was 32 weeks and mean birthweight was 1392 g (Table 1). The majority of the subjects with single pregnancy (82.1%) did not receive resuscitation until they were given positive pressure ventilation (70.2%). 23.3% neonates did have the maternal risk factor of PROM. Proportions for etiology of respiratory distress in our study were sepsis (81.3%), respiratory distress syndrome

Table 1. Baseline Characteristics of the Subjects.

Characteristics	CPAP failure (n=53)	CPAP success (n=97)	P
Gestational age; median IQR	32 (29-33.5)	32 (31-33)	.091[a]
Birth weight; median IQR	1392 (1100-1698)	1474 (1279-1699)	.082[a]
Intrauterine growth in weight; n (%)			
SGA	9 (17.0)	19 (19.6)	.850
AGA	43 (81.1)	77 (79.4)	
LGA	1 (1.9)	1(1.0)	
Multiple birth; n (%)			
Singleton	49 (92.5)	74 (76.3)	.046
Twins	4 (7.5)	22 (22.7)	
Triplets	0 (0)	1 (1)	
Sex; n (%)			
Boys	31 (58.5)	48 (49.5)	.291
Girls	22 (41.5)	49 (50.5)	
PPV during resuscitation; n (%)			
Yes	21 (39.6)	24 (24.7)	.057
No	32 (60.4)	73 (75.3)	
PROM; n (%)			
Yes	16 (30.2)	29(29.9)	.008
No	37 (69.8)	68 (70.1)	
Sepsis; n (%)			
Yes	48 (90.6)	74 (76.3)	.032
No	5 (9.4)	23 (23.7)	
Hypoglycemia; n (%)			
Yes	17 (32.1)	13 (13.4)	.006
No	36 (67.9)	84 (86.6)	
Hypothermia; n (%)			
Yes	33 (62.3)	56 (57.7)	.589
No	20 (37.7)	41 (42.3)	
Type of respiratory distress; n (%)			
RDS	37 (69.8)	47 (48.5)	.008
Neonatal pneumonia	14 (26.4)	30 (30.9)	
TTN	2 (3.8)	20 (20.6)	
CHD; n (%)			
Large PDA	3 (5.7)	3 (3.1)	.253
Moderate PDA	5 (9.4)	3 (3.1)	
Small PDA	1 (1.9)	4 (4.1)	
Other CHD	0 (0.0)	3 (3.1)	
No CHD	44 (83.0)	84 (86.6)	
1-minute APGAR; median IQR	6 (4-7)	6 (5-7)	.011[a]
5-minute APGAR; median IQR	8 (7-9)	8 (7-9)	.023[a]

Abbreviations: AGA, appropriate for gestational age; CHD, congenital heart disease; CPAP, continuous positive airway pressure; IQR, interquartile range; LGA, Large for gestational age; PDA, patent ductus arteriosus; PROM, premature rupture of membrane; PPV, positive pressure ventilation; RDS, respiratory distress syndrome; SGA, small for gestational age; TTN, transient tachypnea of the newborn.
[a]Mann Whitney test.

(RDS) (37.3%), hypothermia (33.3%), neonatal pneumonia (29.3%), and hypoglycemia (20%), respectively.

Study Outcomes

Overall, CPAP occurred in 53 (35%) neonates. Bivariate analysis revealed that infants with birth weight <1000 g significantly influenced CPAP failure (P=.010; OR 12.57; CI 95% 1.42-111.19). Single birth significantly affected CPAP failure (P=.046; OR 3.80; CI 95% 1.24-11.68). An initial Downes score >3 also significantly prompted CPAP failure (P=.001; OR 2.11; IK 95% 1.69-7.67). Likewise, the initiation of FiO_2 requirement ≥30% was susceptible to induce CPAP failure

Table 2. Prediction of Nasal CPAP Failure.

Predictor	CPAP failure n (%)	CPAP success n (%)	Bivariate analysis P	Bivariate analysis OR (95% CI)	Multivariate analysis P	Multivariate analysis Adj OR (95% CI)
Gestational age						
<32 weeks	34 (37.8)	56 (62.2)	.443	1.31 (0.65-2.61)		
≥32 weeks	19 (31.7)	41 (68.3)				
Multiple birth						
Singleton	49 (92.5)	74 (76.3)				
Gemelli	4 (7.5)	22 (22.7)	0.046	3.80 (1.24-11.68)	.026	4.47 (1.19-16.7)
Triplet	0 (0)	1 (1.0)				
Birth weight						
<1000 g	6 (85.7)	1 (14.3)	.010ᵃ	12.57 (1.42-111.19)	0.022	11.55 (1.18-112.45)
1000-1499 g	26 (33.3)	52 (66.7)	.897	1.04 (0.52-2.11)	.981	1.04 (0.45-2.36)
≥1500 g*	21 (32.3)	44 (67.1)				
Antenatal steroids						
Not received	21 (30.9)	47 (69.1)	.419	0.63 (0.21-1.90)		
Partial dose	7 (33.3)	14 (66.7)	.618	0.71 (0.19-2.68))		
Full dose	18 (40.9)	26 (59.1)	.985	0.98 (0.31-3.08)		
No indication*	7 (41.2)	10 (58.8)				
1-minute APGAR score						
<3	6 (54.5)	5 (45.5)	.028	10.20 (1.54-67.217)	.079	6.84 (0.822-57.05)
4-7	45 (37.5)	75 (62.5)	.021	5.10 (1.12-23.11)	.211	2.96 (0.54-16.24)
>7*	2 (10.5)	17 (89.5)				
PROM						
Yes	12 (50.0)	12 (50.0)	.101	1.01 (0.48-2.10)	.790	1.13 (0.45-2.79)
No	41 (32.5)	85 (67.5)				
Initial Downes score						
>3	23 (57.5)	17 (42.5)	.001	3.60 (1.69-7.67)	.035	2.68 (1.07-6.72)
0-3	30 (27.3)	80 (72.7)				
CHD						
PDA	9 (47.4)	10 (52.6)	.271	1.71 (0.65-4.54)		
Not PDA	0 (0.00)	3 (100.0)	.550ᵃ	–		
No CHD*	44 (34.4)	84 (65.6)				
Initiatial FiO₂ requirement						
≥30%	24 (77.4)	7 (22.6)	.0001	10.64 (4.15-27.24)	.0001	8.65 (3.10-24.11)
<30%	29 (24.4)	90 (75.6)				

Abbreviations: CHD, congenital heart disease; CI, confidence interval; CPAP, continuous positive airway pressure; FiO2, fractional concentration of inspired oxygen; OR, odds ratio; PDA, patent ductus arteriosus; PROM, premature rupture of membrane.
Chi-square, ᵃFisher exact test, *Reference.

($P = .0001$; OR 10.64; CI 95% 4.15-27.24). Multivariate analysis included the significant bivariate test with $P < .25$, which compared birth weight, multiple birth, reception of positive pressure ventilation during resuscitation, PROM, sepsis hypoglycemia, type of respiratory distress, APGAR scores at 1-minute, initial Downes score, and initiation FiO₂ requirement. Based on bivariate analysis, there were collinearities between PPV and APGAR score, hypoglycemia and birth weight, type of respiratory distress and hypothermia, hypoglycemia, birth weight, sepsis, and birth weight. The results of the effect of the significant independent variables on nasal CPAP failure were further analyzed using the logistic regression backward method (Table 2).

The most influential factors on nasal CPAP failure were birth weight <1000 g, singleton, Downes score and initiation FiO₂ requirement ≥30% ($P < .05$). Birth weight <1000 g, initial Downes score >3, and initiation FiO₂ requirement ≥30% proved to be significant as the predictor factors of nasal CPAP failure with

($P = .022$; OR 11.55; CI 95% 1.18-112.45), ($p = .026$; OR 4.47; CI 95% 1.19-16.7), ($P = .035$; OR 2.68; CI 95% 3.10-24.11), and ($P = .0001$; OR 8,65; CI 95% 3.10-24.11) respectively. Meanwhile, APGAR scores and PROM were not statistically significant ($P > .05$).

Discussion

Although nasal CPAP was effective as an initiation for initial respiratory support, some preterm infants require higher mechanical ventilation modes or intubation in the first 72 hours of life. We found 35% of infants with nasal CPAP failure, most of whom were singletons, had birth weight <1000 g, initial Downes >3 and initiation FiO_2 requirement ≥30%.

In our study, infants with gestational age ≤32 weeks had nasal CPAP failure (37.8%), but did not show significant differences ($P = .443$). It was probably due to the small number of our sample and the variability of subjects. 40% of our subjects had average gestational age of ≥32, while the reports by Dargaville et al,[5] Bhat et al,[6] and Arora et al,[7] showed the average gestational age of 32 weeks. The majority of our subjects (92.5%) with singleton had a risk of nasal CPAP failure 4.47 times than twins.

Most infants with birth weight <1000 g had nasal CPAP failure (85.7%) compared with those whose birth weight were 1000 to 1499 g (33.3%) and ≥1500 g (32.3%), and there was a statistically significant difference between birth weight <1000 g and birth weight ≥1500 g ($P = .022$). Birth weight <1000 g had 11.55 times higher risk to have nasal CPAP failure. This result was different from the study conducted by Koti et al,[3] in which 53% of infants experiencing nasal CPAP failure had very low birth weight. Another study conducted by Ammari et al[8] also proved that extreme low birth weight, gestational age less than 26 weeks, severe RDS on the initial chest X-ray, and the need for positive pressure ventilation at birth were the predictors of nasal CPAP failure.

The proportion of antenatal steroid received in full dose, partial dose and not received was balanced. 40.9% of infants who received full dose of antenatal steroids, those who received partial dose (33.3%), those who did not receive antenatal steroid (30.9%), and those who were not indicated for antenatal steroids (41.2%) developed nasal CPAP failure. There were no significant differences among the group receiving partial doses, the group with no indication ($P = .618$), and the one which received full dose with no indication of antenatal steroid ($P = .985$). The greater proportion of gestational age made this variable an insignificant predictor. This finding was different from that in the study by Koti et al,[3]

Pillai et al,[9] and Arora et al,[7] which claimed no antenatal steroid was proven to be a predictor of nasal CPAP failure. Based on standard operating procedures in the Department of Obstetrics and Gynecology of Dr. Sardjito Hospital, women with gestational age $24+^0$ to $33+^6$ weeks with PROM received antenatal steroids. In the previous studies, the research subjects were infants with smaller gestational age (less than 34 weeks). The proportion of infants with no indication of antenatal steroid in this study that showed nasal CPAP failure was 41.2%.

Nasal CPAP failure with APGAR score <3 in the first minute was 54.5%, APGAR score 4-7 was 37.5%, and APGAR score 7> was 10.5%. This result was different from the study conducted by Afjeh et al,[10] which showed 1-minute APGAR score was a predictor of CPAP failure in infants with very low birth weight and RDS. In our study, APGAR score was significantly related with CPAP failure based on bivariate analysis, but in multivariate analysis is did not proved to be a significant predictor of nasal CPAP failure.

57.5% of infants with initial Downes score >3 experienced nasal CPAP failure, which was showed significant contribution ($P = .035$) by multivariate analysis. Downes score >3 could predict CPAP failure 2.68 times more than Downes score <3. This result was consistent with that of Koti et al study, showing Downes score as the predictor factor of CPAP failure. Downes score could be used in clinical diagnosis to determine hypoxemia in respiratory distress with sensitivity 88% and specificity 81%. The study conducted by Rusmawati et al[11] revealed hypoxia occurred at PO_2 50 mmHg levels and Downes score ≥ 5.[12]

The proportion of nasal CPAP failure in infants with PDA was 47.4% ($P = .271$). A total of 33.4% of infants were with other CHD and 33.4% without CHD had nasal CPAP failure ($P = .550$). The results of our study were different from those of the study conducted by Koti et al,[3] which showed PDA as one of the factors that influenced of CPAP failure. What distinguished our study from the previous research were the proportion and variability of the research subjects, determined PDA, VSD, and ASD. The definition of CPAP failure in our study was 72 hours, while in the study by Koti et al,[3] it was 1 week of life.

A large majority (77.4%) of infants with initiation FiO_2 requirement ≥30% had nasal CPAP failure. Initiation of FiO_2 requirement ≥30% proved to be a significant predictor factor of nasal CPAP failure ($P = .0001$), which was consistent with the studies conducted by Koti et al,[3] and Pillai et al.[9] The study by Koti et al[3] reported that 25% infants who had no or partial exposure to antenatal steroids, white-out chest X-ray, PDA, sepsis/pneumonia and FiO_2 requirement after

initial stabilization developed CPAP failure. Similarly, Hameed et al[13] reported the variables associated with failure of CPAP were: birth weight <1500 g, gestational age <30 weeks, white out on the cest X-ray, $FiO_2 \geq 50\%$ at 20 minutes of CPAP, and $PEEP \geq 5.5$ cm H_2O. The results of the study by Pillai et al[9] revealed gestational <28 weeks, premature rupture of membranes, product of CPAP pressure, and $FiO_2 \geq 1.28$ at initiation to maintain saturation between 88% and 93% were the independent predictors of failure.

The limitation of our study was the retrospective design used the secondary data from the medical records, thus leading to the inaccuracy of data measurement related to the use of bubble CPAP and ventilator CPAP as well as having some incomplete medical record data.

Conclusion

Birth weight <1000 g, singleton, initial Downes score and initiation of FiO_2 requirement $\geq 30\%$ were the significant predictors of nasal CPAP failure in preterm infants with respiratory distress.

Author Contributions

All authors participated in the study design and interpretation data. Winda Intan Permatahati conseptualized and designed the study, design the data collection instrument, coordinated and supervised data collection, acquisition of data, analysis and interpretation of data, as well as drafted the article. Amalia Setyati conseptualized and designed the study, and carried out initial analysis of the study. Ekawaty Lutfia Haksari conseptualized and designed the study, carried out analysis and interpretation of the data, and drafted initial article and conducted critical review.

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