

Predictors of Early Nasal Continuous Positive Airway Pressure (CPAP) Failure and Consequences in Preterm Infants in Thammasat University Hospital

Sariya Sahussarungsi MD*,
Wilaiporn Techasatid MD*

*Department of Pediatrics, Faculty of Medicine, Thammasat University, Pathumthani, Thailand

Background: Preterm infants are increasingly using nasal continuous positive airway pressure (CPAP) immediately after birth as an initial respiratory support. Some infants managed with this modality ultimately fail on CPAP and require intubation and ventilation. Infants who fail CPAP are associated with a higher risk of adverse outcomes.

Objective: To identify the incidence, predictors and neonatal outcomes associated with the CPAP failure in preterm infants with respiratory distress syndrome (RDS).

Material and Method: Preterm infants of 25 to 32 weeks gestation with RDS receiving nasal CPAP as an initial respiratory support were included in the study. They were divided into two groups according to success or failure on CPAP in the first 72 hours of life. Predictors of CPAP failure were determined and outcomes between the two groups were compared.

Results: CPAP failure occurred in 18 of total 83 infants (22%). Which was more likely to occur at gestational ages of 25 to 28 weeks than at 29 to 32 (50% vs. 15%, $p = 0.005$). In multivariate logistic analysis, gestational age lower than 28 weeks, received positive pressure ventilation in the delivery room, required maximum $FiO_2 \geq 0.5$ and male gender were significantly associated with CPAP failure [adjusted odd ratio 8.53 (95% CI 1.94, 37.50), 3.56 (95% CI 0.83, 15.40), 3.28 (95% CI 0.72, 15.02) and 2.50 (95% CI 0.63, 9.89) respectively]. Infants who failing CPAP had higher mortality (adjusted odd ratio 45.5, 95% CI 2.78, 744.18) and adverse outcomes including BPD (adjusted odd ratio 1.5, 95% CI 0.34, 6.56) and NEC (adjusted odd ratio 1.8, 95% CI 0.18, 18.45) when controlled for gestation and presence of moderate to severe RDS on initial chest radiography.

Conclusion: CPAP failure in preterm infants with RDS usually occurs in those who are born very premature with moderate to severe RDS as indicated by requirement of maximum $FiO_2 \geq 0.5$ in the first hours of life.

Keywords: Preterm infants, Respiratory distress syndrome, Continuous positive airway pressure, Bronchopulmonary dysplasia

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Respiratory distress syndrome (RDS) is a critical predictor of morbidity and mortality in preterm infants. The diagnosis of RDS can be confirmed by chest radiography showing a classical 'ground glass' appearance and air bronchograms. If left untreated, death may occur from progressive hypoxia and respiratory failure. Current practice guidelines in neonatology recommend using CPAP immediately after birth with subsequent selective surfactant administration should be considered as an alternative to routine intubation with prophylactic or early

surfactant administration⁽¹⁾. Recently large, multicenter randomized controlled trials of prophylactic or early nasal CPAP in preterm infants ≤ 29 weeks' gestation have indicated that when CPAP is started soon after birth, it is associated with equivalent or superior respiratory outcomes, as compared to infants who are intubated and received prophylactic surfactant⁽²⁻⁴⁾. However, not all extremely premature infants with RDS who are given CPAP can be successfully managed with this modality. Infants who fail on CPAP may suffer the consequences of delayed surfactant administration and other adverse related outcome. Several studies have suggested that infants who failed CPAP are associated with a higher risk of adverse outcomes, including death, bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH), and necrotizing enterocolitis (NEC) than those with successful CPAP⁽⁵⁻⁹⁾.

Correspondence to:

Techasatid W, Department of Pediatrics, Faculty of Medicine, Thammasat University, 95 Paholyothin Road, Klongluang, Pathumthani 12120, Thailand.

Phone: +66-89-0339442, Fax: +66-82-9269513

E-mail: wilaiporn66@gmail.com

The authors aimed to determine the incidence of CPAP failure and explore the early predictors of CPAP failure including demographic risk factors and clinical indices of respiratory function, and the adverse outcomes in CPAP failure infants.

Material and Method

This was the retrospectively review of data between October 2014 and October 2016. The study was approved by the Ethics Committee of the Faculty of Medicine, Thammasat University. Our NICU (Neonate Intensive Care Unit) uses CPAP as an initial respiratory support for 25 to 32 weeks gestation infants with respiratory distress, with a maximum CPAP pressure of 7 cm H₂O and FiO₂ 0.4 to 0.6. If the FiO₂ requirement exceeds 0.6, or ventilation appears inadequate (arterial pH <7.20 and PaCO₂ >60 mmHg), or infants developed frequent episodes of apnea requiring repeated bag and mask ventilation despite adequate CPAP delivery and oxygenation during the first 72 hours of life, the infants will then receive endotracheal intubation and exogenous surfactant.

Study population

Our study included infants born at our hospital with gestational age of 25 to 32 weeks by best obstetric estimate who were admitted to the NICU with respiratory distress and managed initially with early nasal CPAP. Infants requiring intubation in the delivery room or shortly after arrival in the NICU were excluded.

Data collection

Clinical indices of respiratory function were defined from the intensive care charts. Data recorded included maximum FiO₂ (sustained for at least 15 min) and CPAP pressure in the first 2 to 6 hours of life. CPAP failure was defined as the need for intubation before 72 hours, and the radiological severity of RDS was categorized by the attending physicians as mild, moderate or severe⁽¹⁰⁾. The radiographic finding was classified as moderate or severe if it show dense reticulogranular pattern making the borders of the heart, thymus and diaphragm unclear or impossible to distinguish the borders with an air bronchogram seen in the major parts of the bronchi and the trachea. Demographic and clinical outcomes were collected from our unit's databases including gestational age, sex, birth weight, route of delivery, administration of prenatal steroids, presence of multiple births, Apgar scores, and delivery room management (positive pressure ventilation via a bag and mask) (PPV). The adverse

outcomes included death, bronchopulmonary dysplasia (BPD), defined as the need for supplementary oxygen or any form of respiratory support at 36 weeks post-menstrual age, necrotizing enterocolitis (NEC) stage >2 by Bell's staging system⁽¹¹⁾, retinopathy of prematurity (ROP) as defined by the International Classification of Retinopathy of Prematurity classification⁽¹²⁾, all grades of intraventricular hemorrhage (IVH) by Papile's classification⁽¹³⁾, duration of hospital stay (days) and duration of oxygen support (days).

Statistical analysis

Baseline characteristic risk factors and outcome variables were compared between infants who succeeding and failing in early nasal CPAP. Data were expressed as means and standard deviations for normal distributions. Comparable categorical data between the two groups were analyzed using the Chi-square test or Fischer's exact test when appropriate. Comparable continuous data between the two groups were analyzed using an independent sample T test or Mann-Whitney U test. A *p*-value less than 0.05 was considered significant. Logistic regression models were used to investigate the effects of clinical indices of respiratory function coupled with potential demographic predictors.

Results

A total of 83 infants of 25 to 32 weeks gestation were treated initially with early nasal CPAP. Overall, CPAP failure occurred in 18 infants (22%). There was 100% CPAP failure in infants at gestation of 25 weeks. Occurrence was more likely at 25 to 28 weeks gestation than at 29 to 32 (50% vs. 15% *p* = 0.005). The proportion of CPAP failure was higher in infants with lower birth weight (28%, 30% and 12% in 500-999, 1,000-1,499 and 1,500-2,000 g, respectively), (Table 1). There were no differences in birth weight, sex, cesarean delivery, multiple birth and reception of prenatal steroids between the two groups (Table 2). In univariate logistic regression analysis, there was increased risk of CPAP failure in lower than 28 weeks gestation, male, required PPV in the delivery room, presence of moderate to severe RDS on initial chest radiography and requirement of FiO₂ ≥0.5 in the first hours of life infants (Table 3). In the multivariate logistic analysis, gestational age lower than 28 weeks, received positive pressure ventilation in the delivery room, required maximum FiO₂ ≥0.5 and male gender were significantly associated with CPAP failure [adjusted odd ratio 8.53

Table 1. Proportion of infants with CPAP failure by distribution of gestational age and birth weight

	Gestational age (week)			Birth weight (g)	
	25 to 28	29 to 32	500 to 999	1,000 to 1,499	1,500 to 2,000
No of infants	16	67	7	36	40
CPAP failure, n (%)	8 (50)	10 (15)*	2 (28)	11 (30)	5 (12)

* The *p*-values = 0.005 by Fischer's exact test

Table 2. Baseline characteristics

	CPAP success n = 65	CPAP failure n = 18	<i>p</i> -value
Male, n (%)	31 (48)	11 (61)	0.426
BW (g), median (IQR)	1,526 (1,258, 1,662)	1,340 (1,128, 1,586)	0.237
GA (week), median (IQR)	31 (30 to 32)	30 (28 to 32)	0.027
Multiple birth, n (%)	20 (31)	3 (17)	0.373
Cesarean section, n (%)	38 (58)	8 (44)	0.422
5 minutes apgar score, median (IQR)	10 (8 to 10)	10 (8 to 10)	0.622
Received prenatal steroid, n (%)	48 (74)	12 (67)	0.562

Table 3. Prediction of CPAP failure

Predictors	Univariate logistic regression		
	Odds ratio	95% CI	<i>p</i> -value
Gestational age <28 weeks	5.70	1.73, 18.70	0.004
Birth weight <1,000 g	1.50	0.26, 8.46	0.646
Male	1.72	0.59, 5.00	0.317
Caesarean delivery	0.56	0.19, 1.62	0.293
Multiple birth	0.45	0.12, 1.73	0.245
Prenatal steroids (any)	0.70	0.28, 2.18	0.548
Required PPV in delivery room	2.40	0.76, 7.95	0.134
Presence of mod-severe RDS*	16.57	4.72, 58.14	<0.001
CPAP level	0.64	0.19, 2.19	0.478
Required maximum FiO ₂ ≥ 0.5	4.28	1.18, 15.48	0.026

* Presence of moderate to severe RDS on initial chest radiography

(95% CI 1.94, 37.50), 3.56 (95% CI 0.83, 15.40), 3.28 (95% CI 0.72, 15.02) and 2.50 (95% CI 0.63, 9.89) respectively] (Table 4). The adjusted odd ratios for the logistic regression models for mortality and morbidity for those who failed CPAP is shown (Table 5). The models were controlled for gestation and presence of moderate to severe RDS on initial chest radiography. Infants failing CPAP had higher mortality (adjusted odd

ratio 45.5, 95% CI 2.78, 744.18), BPD (adjusted odd ratio 1.5, 95% CI 0.34, 6.56) and NEC (adjusted odd ratio 1.8, 95% CI 0.18, 18.45). The hospital stay in the CPAP failure group were 50 (19, 60) days compared to 31 (21, 44) days (median, interquartile range, *p* = 0.685) in the CPAP success group. The duration of oxygen support was significantly higher in the CPAP failure group 32 (8, 49) days compared to 7 (3, 20) days (median, interquartile

Table 4. Multivariate logistic regression of predictors of CPAP failure

Predictors	Adjusted odds ratio	95% CI	<i>p</i> -value
Gestational age <28 weeks	8.53	1.94, 37.50	0.005
Required maximum FiO ₂ ≥0.5	3.28	0.72, 15.02	0.125
Required PPV in delivery room	3.56	0.83, 15.40	0.087
Male	2.50	0.63, 9.89	0.192

Table 5. Adverse outcomes for CPAP failure infants

Adverse outcomes	Odds ratio	95% CI	<i>p</i> -value	Adjusted odds ratio*	95% CI	<i>p</i> -value
Death	12.8	1.22, 131.81	0.032	45.5	2.78, 744.18	0.007
NEC	1.5	0.26, 8.46	0.646	1.8	0.18, 18.45	0.603
BPD	3.3	1.12, 9.90	0.030	1.5	0.34, 6.56	0.586
IVH	0.95	0.72, 3.33	0.939	0.57	0.11, 3.08	0.522

BPD = bronchopulmonary dysplasia; IVH = intraventricular haemorrhage; NEC = necrotizing enterocolitis

* Adjusted odds ratio for gestation and presence of moderate to severe RDS on initial chest radiography

range, *p* = 0.022) in the CPAP success group.

Discussion

In our study, most spontaneously breathing preterm infants (78%) were managed successfully with early nasal CPAP. Even in the lower gestation (25 to 28 weeks), CPAP was successful in about half of the infants. In the 25 to 28 weeks gestation range, the CPAP failure rate (50%) was comparable to previous studies (25 to 50%)^(5,9). Except for male gender and gestational age, our data did not support the finding of the other demographic factors as a predictor. Some infants on CPAP managed without an indwelling arterial catheter which may limit the evaluation of oxygen indices in arterial blood gas. Therefore, the highest level of FiO₂ in the 2 to 6 hours of life was used as the indicator of oxygenation to predict CPAP failure. We found that factors associated with CPAP failure were those related to immaturity, male, reception of PPV in the delivery room and requirement of maximum FiO₂ ≥0.5 in the first hours of life. These factors define cases with small baby that born very premature who required positive pressure ventilation in the delivery room with unremitting RDS where the condition can be expected to progress as indicated by requirement of maximum FiO₂ ≥0.5 in the first hours of life. In our study, the data support the previous studies^(5,9) that infants failing CPAP in the first 72 hours have a higher rates of mortality

and adverse outcomes. The clinical outcomes for infants who succeed on CPAP are excellent with lower mortality, BPD, NEC, the duration of oxygen support and hospital stay. According to the high mortality rates in the failing CPAP group, it might be wrong to continue CPAP in any infant with the factors that associated with CPAP failure.

Conclusion

Preterm infants with RDS whom receiving nasal CPAP as an initial respiratory support, gestational age lower than 28 weeks, received PPV in the delivery room, required maximum FiO₂ ≥0.5 and male gender appeared to be a good predictor of CPAP failure.

What is already known on this topic?

Widespread use of nasal CPAP as the initial respiratory support modality in preterm infants with RDS is progressively replacing intubation and mechanical ventilation. Some infants will develop worsening respiratory failure and eventually require intubation. Infants who failed CPAP are associated with a higher risk of adverse outcomes.

What this study adds?

Preterm infants failing CPAP usually occurs because of worsening respiratory distress syndrome. An indicator of oxygenation such as requirement of

maximum $\text{FiO}_2 \geq 0.5$ is the good predictor of CPAP failure.

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Potential conflict of interest

None.

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ปัจจัยที่สามารถพยากรณ์โอกาสเกิดภาวะล้มเหลวจากการช่วยหายใจด้วย continuous positive airway pressure ทันทีหลังเกิด
ในทารกเกิดก่อนกำหนดในโรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ

ศรียา สหัสสรังษ์, วิไลพร เตชะสาริต

ภูมิหลัง: ทารกเกิดก่อนกำหนดมักเกิด respiratory distress syndromes (RDS) ที่ต้องการการช่วยหายใจทั้งแบบ continuous positive airway pressure (CPAP) หรือใส่เครื่องช่วยหายใจหลังเกิดขึ้นกับความรุนแรงของโรค การช่วยหายใจด้วย CPAP ทันทีหลังเกิดในทารกเกิดก่อนกำหนดที่มี RDS ถือเป็นแนวปฏิบัติที่มีมาตรฐานและมีผลแทรกซ้อนน้อย ทารกบางรายอาจมีการดำเนินโรคที่รุนแรงไม่ตอบสนองต่อ early nasal CPAP เกิดภาวะหายใจล้มเหลวและต้องการการใส่ท่อช่วยหายใจในระยะต่อมา (CPAP failure) ทำให้ทารกได้รับความเสี่ยงต่อการได้รับการรักษาที่ล่าช้าและมีความเสี่ยงต่อการเกิดภาวะแทรกซ้อนเกิดภาวะทุพพลภาพตามมา

วัตถุประสงค์: ศึกษาอุบัติการณ์การเกิดภาวะ CPAP failure ปัจจัยที่สามารถพยากรณ์การเกิดภาวะ CPAP failure ในทารกเกิดก่อนกำหนดที่ช่วยหายใจด้วย early nasal CPAP ตลอดจนถึงผลการรักษาและภาวะแทรกซ้อนในทารกกลุ่มที่เกิดภาวะ CPAP failure เปรียบเทียบกับกลุ่มที่ประสบความสำเร็จ (CPAP success)

วัสดุและวิธีการ: ทารกเกิดก่อนกำหนดอายุครรภ์น้อยกว่าหรือเท่ากับ 32 สัปดาห์ ในหอบริบาลทารกแรกเกิดวิกฤติ โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติในช่วงปี พ.ศ. 2557 ถึง พ.ศ. 2559 ที่มีภาวะหายใจลำบาก (RDS) ได้รับการรักษาด้วย early nasal CPAP ทันทีหลังเกิดและได้รับการติดตามใน 72 ชั่วโมงแรกโดยแบ่งทารกเป็นสองกลุ่มคือ กลุ่มที่ success CPAP และกลุ่มที่ fail CPAP ศึกษาเปรียบเทียบปัจจัยที่ใช้คาดการณ์การเกิดภาวะ CPAP failure เช่น อายุครรภ์ น้ำหนักแรกคลอด เพศ การผ่าตัดคลอด การได้รับสเตียรอยด์ก่อนคลอด การได้รับการช่วยหายใจด้วยแรงดันบวกขณะช่วยกู้ชีพ ความรุนแรงของ RDS จากภาพถ่ายรังสีทรวงอกและค่า FiO_2 ที่ใช้สูงสุดใน 2 ถึง 6 ชั่วโมงแรก

ผลการศึกษา: ทารก 83 ราย พบภาวะ CPAP failure 18 ราย (ร้อยละ 22) โดยพบร้อยละ 50 ในทารกช่วงอายุครรภ์ 25 ถึง 28 สัปดาห์และร้อยละ 15 ในทารกช่วงอายุครรภ์ 29 ถึง 32 สัปดาห์ ปัจจัยที่ใช้ในการคาดการณ์การเกิดภาวะ CPAP failure คือ อายุครรภ์ที่น้อยกว่า 28 สัปดาห์ การได้รับการช่วยหายใจด้วยแรงดันบวกขณะช่วยกู้ชีพ ทารกที่ต้องการออกซิเจนสูงมากกว่าร้อยละ 50 ใน 2 ถึง 6 ชั่วโมงแรกและทารกเพศชายโดยมีค่า adjusted odd ratio และค่า 95% CI เท่ากับ 8.53 (1.94, 37.50), 3.56 (0.83, 15.40), 3.28 (0.72, 15.02) และ 2.50 (0.63, 9.89) ตามลำดับ พบอัตราตายและความเสี่ยงในการเกิดโรคปอดเรื้อรัง (BPD) และโรคลำไส้เน่าตาย (NEC) เพิ่มขึ้นในทารกที่ไม่ตอบสนองต่อการรักษาด้วย early nasal CPAP โดยมีค่า adjusted odd ratio และค่า 95% CI 45.5 (2.78, 744.18) 1.5 (0.34, 6.56) และ 1.8 (0.18, 18.45) ตามลำดับ

สรุป: ปัจจัยที่สามารถใช้คาดการณ์การเกิดภาวะ CPAP failure ในทารกที่ได้รับการรักษาภาวะหายใจลำบากด้วย early nasal CPAP ได้แก่ อายุครรภ์ที่น้อยกว่า 28 สัปดาห์ เพศชาย การได้รับการช่วยหายใจด้วยแรงดันบวกขณะช่วยกู้ชีพ และการต้องการออกซิเจนสูงมากกว่าร้อยละ 50 ใน 2 ถึง 6 ชั่วโมงแรก
