Early nasal continuous positive airway pressure failure prediction in preterm infants less than 32 weeks gestational age suffering from respiratory distress syndrome

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Short title: Continuous positive airway pressure failure in respiratory distress syndrome

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Abstract

Background: Early continuous positive airway pressure (CPAP) and surfactant replacement are effective treatments for neonatal respiratory distress syndrome (RDS). CPAP is first-line in preterm infants needing respiratory support, with surfactant replacement in case of CPAP failure (CPAP-F).

Objectives: To analyze incidence and factors associated with CPAP-F in preterm infants with RDS.

Design and setting and patients: Single-center, retrospective database analysis (2004–2017) of inborn infants, gestational age (GA) 24+0/7 to 31+6/7 weeks, not intubated on admission to the neonatal intensive care unit, managed with CPAP. CPAP-F was defined as intubation and surfactant administration in the first 72 hours of life; CPAP success (CPAP-S) was CPAP alone without need for additional RDS treatments. Demographic, respiratory and clinical data associated with CPAP-F were studied using logistic regression analysis.

Results: A total of 562 infants met the inclusion criteria: 252 (44.8%) were CPAP-F and 310 (55.2%) were CPAP-S. The CPAP-F, compared to CPAP-S group, had lower GA and birth weight, and were less likely to receive antenatal steroids or to be vaginal births. Logistic regression showed that the fraction of inspired oxygen (FiO_2)≥0.23 between 180–240 minutes of life (FiO_2 180–240') was the strongest factor associated with CPAP-F (OR 16.01 [95% CI 10.34–24.81]).

Conclusion: FiO_2 180–240' was highly predictive of CPAP-F in preterm infants. With this model for surfactant administration/CPAP-F, 11.2% of infants would have unnecessarily received treatment, but importantly 27.7% would have been treated much earlier, with a potential reduction in air leaks and duration of mechanical ventilation.

Introduction

Exogenous surfactant therapy is an effective treatment for neonatal respiratory distress syndrome (RDS), reducing both the severity of respiratory distress and mortality, especially in very low birth weight (BW) preterm infants [1–3]. Prophylactic surfactant administration has similar efficacy to early nasal continuous positive airway pressure (CPAP) in terms of mortality or bronchopulmonary dysplasia (BPD), especially in preterm infants who have mostly received antenatal steroids (ANS) [4–8]. Importantly, however, compared with later administration, early surfactant treatment decreases the risk of air leak, mortality, BPD, and the duration of mechanical ventilation (MV) [9–12].

Several factors are associated with CPAP failure (CPAP-F), including low BW, low gestational age (GA), male gender [13–16], cesarean section (CS) [15] or Apgar score [13–15], but the role of early predictors is not clear. Different studies examining the fraction of inspired oxygen (FiO_2) in the first hours of life to predict CPAP-F produced variable results [17–20]. Furthermore, the optimal FiO_2 threshold for surfactant administration is still unclear [13,14,16,17,21] because all these studies not reach the same result.

In the 2019 the European guidelines on the management of RDS (21), have suggested a uniform FiO2 threshold of >0.30 for surfactant administration for all gestational age (GA), differently from the version before (22), but this is based on an expert consensus, not on a clinical trial.

In the current study, we analyzed the incidence and factors associated with CPAP-F in a very large cohort of preterm infants born in Marche Region (Italy) to identify early predictors of CPAP-F.

Materials and methods

Study design

This was a retrospective database analysis. Data were collected prospectively into the database according to predefined definitions, which did not change during the study period.

Participants

We included all consecutive admissions to our regional neonatal intensive care unit (NICU), from January 2004 to December 2017 of inborn preterm infants with GA between 24+0/7 and 31+6/7 weeks, managed with CPAP as primary respiratory support for neonatal RDS. All infants born in the Marche region with GA of less than 32 weeks are either born at or immediately transferred after birth to our center. Exclusion criteria from the current analyses were: 1) BW < 400 g; 2) major congenital malformations; 3) endotracheal intubation at admission; 4) endotracheal intubation for non-respiratory indications (surgery or sepsis); 5) no ventilatory support during the first 3 days; 6) start of CPAP support after 3 hours of life; 7) violations of the institutional protocol for surfactant administration; 8) incomplete clinical data.

Ventilatory support

In the delivery room, spontaneously breathing preterm infants were started on nasal CPAP (4–8 cmH_2O), using facial mask and T-piece device (Neopuff, Fisher and Pykel, Auckland, New Zealand), with FiO_2 initially set to 0.30 and subsequently adjusted to obtain preductal pulse oxygen saturation values of approximately 90%. Non-invasive positive pressure ventilation by facemask was performed for persistent apnea or bradycardia. Infants were intubated if a preductal pulse oxygen saturation >85% was not reached or resuscitation was needed.

Infants stabilized on CPAP in the delivery room, were transported to the NICU, and were then switched to variable flow (InfantFlow, Care Fusion, Yorba Linda, CA, USA) or constant flow CPAP (Babylog 8000, Draeger Medical, Lübeck, Germany), optimized with a positive end-expiratory pressure (PEEP) of 4–8 cmH_2O. CPAP-F was defined as the need for surfactant administration due to at least one of: 1) FiO_2 > 0.30 and PEEP ≥ 4cmH_2O, to maintain a preductal oxygen saturation of 86–92%, for ≥ 30 minutes; 2) Respiratory acidosis, defined as pH <7.20 with pCO_2 >65mmHg, in arterial or arterialized capillary blood; 3) Apnea unresponsive to stimulation or caffeine. Criteria for exogenous surfactant therapy did not change during the study period.

Patients failing CPAP were intubated for surfactant administration. Neonates were ventilated for the shortest time possible using gentle ventilation.

Poractant-α therapy (Curosurf, Chiesi Farmaceutici SpA, Parma, Italy) was indicated when FiO_2 was > 0.30–0.40 with 10% tolerance. The first dose administered was 100 mg/kg between 2004–2009, and 200 mg/kg between 2010–2017. Subsequent doses were 100 mg/kg throughout the study period [23].

Outcomes

We recorded in the clinical chart the occurrence of major adverse outcomes, defined according with Vermont Oxford Network definitions [24], and death before discharge or at 36 weeks of GA. Outcomes of interest were: duration of MV, pneumothorax, BPD, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH)>II degree, retinopathy of prematurity (ROP) > II degree.

FiO2 data used for this study were collected in the clinical charts of patients hourly from birth to discharge or by electronic records when available. The hourly FiO2 reported was the highest FiO2 (sustained for at least 15 min) in the time epoch recorded, as long as it was not related to pain or suctioning of the infants.

Statistical analysis

Data were tested for normality with the Shapiro-Wilk test, with the results expressed as mean and standard deviation, median and interquartile range, or frequency and percentage. Data were analyzed using Student’s t-test or Wilcoxon rank-sum test for continuous data, and chisquare or Fisher's exact test for categorical variables. A two-tailed p-value <0.05 was considered significant.

A Decision Tree analysis was used to evaluate different dependent variables (FiO_2 between 0.21 to 0.30 in the first six hours of life, GA, BW, gender, type of delivery, 5' Apgar), to identify the best predictive model for early CPAP-F [25]. Resulting outcome values were tested using receiver operating characteristic (ROC) curves. Areas under the curve (AUC), sensitivity and specificity were determined. Statistical analysis was performed using SPSS 23.0 (IBM, Chicago, IL, USA) and MATLAB 8.0 (The MathWorks, Inc., Natick, MA, USA).

Results

From 2004 to 2017, 1444 infants with GA between 24+0/7 and 31+6/7 weeks and BW > 400 g were admitted to our regional NICU, 859 of whom were excluded from these analyses (187 were outborn, 419 were intubated before NICU admission, 148 received no respiratory support in the first three days, 63 started CPAP after 3 hours of life, and 42 had incomplete data). Of 585 eligible patients, 23 were excluded (ten were intubated for surgical reasons, 13 received surfactant off protocol). Five hundred sixty-two patients received CPAP as primary respiratory support for neonatal RDS and met inclusion criteria (Figure 1).

During the study period, there were two epochs 2004–2009 and 2010–2017, corresponding to the routine use of 100 and 200 mg/kg as first dose of exogenous surfactant respectively. There was no difference between these epochs in GA or BW, SGA or multiple birth, and other demographic data, however the incidence of primary intubation, surfactant administration, death, and death or BPD were significantly lower in the second epoch (data not shown). However, in the 562 study patients who could be stabilized on CPAP, the incidence of surfactant administration, BPD, death, and death or BPD did not differ between the epochs (data not shown).

Among the patients stabilized on CPAP, 310 (55.2%) were classified as CPAP success (CPAP-S), and 252 (44.8%) as CPAP-F.

Compared to CPAP-S, the CPAP-F group had lower GA ($p=0.001$), BW ($p=0.019$), and ANS use ($p=0.010$), and were more likely to have been born via CS ($p=0.002$) (Table 1, with the absolute numbers and proportions by GA in Figure 2 A and B, respectively). In addition, the CPAP-F group had a longer duration of respiratory support (either MV or non-invasive ventilation), and higher incidence of adverse outcomes or death than CPAP-S infants (Table 2).

The best predictor of CPAP-F in the Decision Tree analysis was $FiO_2 \geq 0.23$ between 180 and 240 minutes of life (FiO_2 180–240'). The other variables tested were rejected by the statistical model. In the ROC curve analysis, FiO_2 180–240' was also strongly associated with CPAP-F

(AUC 0.86, sensitivity 84%, specificity 80%). Results were similar in the two epochs 2004–2009 and 2010–2017 (AUC 0.83 and 0.84, sensitivity 84% and 79%, specificity 77% and 80%, respectively) and when tested in infants with GA 24–28 weeks and 29–31 weeks (AUC 0.90 and 0.84, sensitivity 88% and 82%, specificity 84% and 79%, respectively).

At the time point between 180-240 minutes of life, CPAP level and the FiO2 were higher in CPAP-F than CPAP-S (6 [4-6] cmH2O vs 4 [4-6] cmH20 respectively, and 0.27 [0.23-0.30] vs 0.21 [0.21-0.21] respectively, p<0.000 and <0.000) and this can reflect a more serious respiratory impairment in CPAP failure group.

At the time point of 180-240 minutes 66 infants were intubated.

The median age at surfactant administration was 7.1 hours [interquartile range (IQR): 3.9–14.3], with median FiO_2 before surfactant administration 0.30 [IQR: 0.30–0.40]. The time delay was calculated between the actual surfactant administration and hypothetical timing based on reaching an FiO_2 180–240'. The median time delay was 6.0 [IQR: 2.0–15.4] hours. Had we used this model for surfactant administration, we would have treated 63 infants (11.2%) who did not actually receive exogenous surfactant, and 156 infants (27.7%) would have been treated at a median of 6.0 [IQR: 2.0–15.4] hours earlier.

After logistic regression FiO_2 180–240' was overall predictive of CPAP-F, either in infants with GA between 24–28 weeks, and in those with GA 29–31 weeks (Table 3).

Discussion

Early CPAP is the preferred strategy for RDS treatment in preterm infants with adequate respiratory drive [22]. However, there is no consensus on early predictors of CPAP-F, perhaps due to heterogeneity of previous study groups and differences in the definition of CPAP-F [17–20]. Dargaville and colleagues [17] found that FiO_2≥0.30 in the first hours of life was a good predictor, whereas De Jaegere et al [18] found a threshold of FiO_2=0.25 in the first two hours was a predictor, and Rocha et al [19] found a threshold of FiO_2=0.25 in the first 4 hours of life had predictive value, but only for male preterm infants, with a threshold of FiO_2=0.40 independent of gender. More recently, Gulczynska and colleagues [20] reported that FiO_2=0.29 in the second hour of life was a good predictor, although unlike in other studies, the CPAP-S group included patients who received early surfactant administration (via less invasive surfactant administration or intubation-surfactant-extubation techniques) and who could be successfully extubated and maintained on CPAP. Finally, in two previous studies alveolar gas exchange did not predict early CPAP-F [15,16], whereas in a third study the alveolar-arterial oxygen tension gradient was a significant predictor [13].

In our study, FiO_2 180–240’ was highly predictive for CPAP-F in infants <32 weeks GA. This threshold appears to be a good predictor both for extremely preterm (≤28 weeks GA), and preterm infants (>28 weeks). In the logistic regression analysis, the most important factor for CPAP-F was FiO_2 180–240’ in both GA groups. Although our data are consistent with previous studies in identifying FiO_2 as the best predictor of CPAP-F, the threshold that we identified was lower than in these previous studies. In our view 180–240 minutes is a reasonable time point to assess FiO_2, as 3–4 h after birth most infants have likely reached “stabilization”. Furthermore, FiO_2 ≥0.23 may represent, in most patients, an early sign of the onset of RDS, typically starting as mild then progressively worsening, and clinically presenting as increased work of breathing, sternal recession and increasing oxygen requirements. As expected, GA impacted the incidence of CPAP-F, becoming less frequent at higher GA. However, it is of interest that infants with lower and higher GA showed a remarkably similar threshold for CPAP-F. This adds further support to our view that this FiO2 threshold typically reflects the early phase of RDS. Our interpretation is that GA affects the incidence of CPAP-F (more cases occur at low GA), but the pattern of oxygen dependency of patients who will eventually develop mild RDS is similar regardless of GA.

Our model predicts the need for surfactant treatment with good sensitivity and specificity (84% and 80%, respectively). Had we used this model for surfactant administration, 11.2% of the infants would have received an unnecessary treatment, but importantly 27.7% would have received surfactant treatment on average six hours earlier than actually happened. Early surfactant initiation in RDS has been shown to reduce the risk of air leak and the duration of MV [10-12], although the cost-benefit of this approach needs further studying. Previous studies found that infants that failed CPAP had a higher rate of adverse outcomes compared with CPAP-S [13-14]. Our results are consistent with these data (Table 3).

We acknowledge several limitations of this study: first, we had a high rate of intubation in the delivery room for the low GA infants (>50% for <28 weeks' GA). This percentage was similar to other studies [15], but higher than in others [13]. This could be partly explained by the distance between the delivery room and the NICU at our institution, and this in turn may have influenced the prediction of CPAP-F by excluding from our CPAP cohort some cases with intermediate severity. Other limitations are the long timespan of the study and the fact that we did not perform early lung ultrasound. The long-time span of the study however can also be viewed as a strength, as the prediction model held true in both study epochs. The change in surfactant dosing between the two epochs (an intervention that occurred after diagnosis of CPAP-F) was not relevant to the purpose of the present study, although we acknowledge that the dose of exogenous surfactant might have influenced some outcome data, as may the long duration of the study. For these reasons, we preferred not to discuss outcomes data. Another point that needs discussion is the FiO2 threshold used for CPAP-F and thus for exogenous surfactant administration (FiO_2 > 0.30 and PEEP ≥ 4cmH_2O). We used a lower FiO2 than other studies and could have resulted in higher CPAP-F rate compared to other studies (13,15,17), but this was not the case (14,16). Some differences among studies may reflect differences in CPAP-F definition and inclusion criteria. Please note that the FiO2 threshold for CPAP-F we have been using at our institution since 2002 was similar to that recommended by the 2019 RDS European guidelines (21). Finally, the retrospective nature of this study is a limitation, although all definitions were pre-specified, data were prospectively collected, and the criteria for surfactant administration used by our center did not change during the study period. Despite these limitations, our predictive model, based on data from 562 infants, shows a better fit than other published studies [13,17,20], with accuracy, sensitivity and specificity being also somewhat better than in other studies. More importantly, our model was valid across different GAs and a relatively long study period. Our model possibly detects the early phase of mild RDS that occurs only in a variable proportion of the patients who will develop the typical clinical pattern of increasing oxygen dependency

Conclusion

In conclusion, in our cohort we found that an FiO2 ≥0.23 at 180–240' was a good predictor of CPAP-F in preterm infants <32 weeks GA and was valid across a wide GA range and two study epochs. The accuracy of this model across GA support the notion that is possible to standardize the FiO_2 threshold for surfactant treatment across GAs from 24 to <32 weeks. We speculate that a lower FiO_2 threshold for surfactant administration could reduce both the delay of treatment and the risk of adverse events.

Further studies are needed to confirm the clinical relevance of our model.

Statement of Ethics

This retrospective evaluation was approved by the Research Institute’s Committee on human research (Comitato Etico Regione Marche) (Det. N160/DG, protocol code 002).

Given the retrospective nature of this study, informed consent was not needed.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author contributions

VDO: writing – original draft (lead); conceptualization (supporting), formal analysis (equal); writing – review and editing (equal)..

PM: formal analysis (lead); writing – review and editing (supporting)

AC, IG, SN formal analysis (equal); writing – review and editing (supporting)

CR, IB, MLP writing – review and editing (supporting)

VPC conceptualization (lead), writing – original draft (lead); conceptualization (lead), formal analysis (equal); writing – review and editing (lead)

All authors approved the final version as submitted.

What is already known on this topic: Early CPAP is the preferred strategy for RDS treatment in preterm infants with adequate respiratory drive. However, there is no consensus on early predictors of CPAP failure regarding the FiO_2 threshold in the first hours of life.

What this study adds: In our study, a $FiO_2 \geq 0.23$ between 180 and 240 minutes of life was highly predictive for CPAP failure in infants <32 weeks GA. It can reflect the onset of RDS and can help to anticipate surfactant administration.

References

1. Engle WA. Surfactant-replacement therapy for respiratory distress in the preterm and term neonate. American Academy of Pediatrics Committee on Fetus and Newborn. Pediatrics. 2008 Feb;121(2):419–32.

2. Jobe AH. Pulmonary surfactant therapy. N Engl J Med. 1993 Mar 25;328(12):861–8.

3. Soll RF, Morley CJ. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2001;(2):CD000510. Review. Update in: Cochrane Database Syst Rev. 2012;3:CD000510.

4. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB; COIN Trial Investigators. Nasal CPAP or intubation at birth for very preterm infants. N Engl J Med. 2008 Feb 14;358(7):700–8

5. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Early CPAP versus surfactant in extremely preterm infants. N Engl J Med. 2010 May 27;362(21):1970–9.

6. Dunn MS, Kaempf J, de Klerk A, de Klerk R, Reilly M, Howard D, et al. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics. 2011 Nov;128(5):e1069–768.

7. Sandri F, Plavka R, Ancora G, Simeoni U, Stranak Z, Martinelli S, et al. Prophylactic or early selective surfactant combined with nCPAP in very preterm infants. Pediatrics. 2010 Jun;125(6):e1402–9.

8. Rojas-Reyes MX, Morley CJ, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev. 2012 Mar 14;(3):CD000510.

9. Konishi M, Fujiwara T, Chida S, Maeta H, Shimada S, Kasai T, et al. A prospective, randomized trial of early versus late administration of a single dose of surfactant-TA. Early Hum Dev. 1992 Jun-Jul;29(1-3):275–82.

10. Plavka R, Kopecky P, Sebron V, Leiská A, Svihovec P, Ruffer J, et al. Early versus delayed surfactant administration in extremely premature neonates with respiratory distress syndrome ventilated by high-frequency oscillatory ventilation. Intensive Care Med. 2002 Oct;28(10):1483–90.

11. Bahadue F L, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Cochrane Database Syst Rev. 2012 Nov 14;11:CD001456.

12. Verder H, Albertsen P, Ebbesen F, Greisen G, Robertson B, Bertelsen A, et al. Nasal continuous positive airway pressure and early surfactant therapy for respiratory distress syndrome in newborns of less than 30 weeks' gestation. Pediatrics. 1999 Feb;103(2):E24.

13. Ammari A, Suri M, Milisavljevic V, Sahni R, Bateman D, Sanocka U, et al. Variables associated with the early failure of nasal CPAP in very low birth weight infants. J Pediatr. 2005 Sep;147(3):341–7.

14. Fuchs H, Lindner W, Leiprecht A, Mendler MR, Hummler HD. Predictors of early nasal CPAP failure and effects of various intubation criteria on the rate of mechanical ventilation in preterm infants of <29 weeks gestational age. Arch Dis Child Fetal Neonatal Ed. 2011 Sep;96(5):F343–7.

15. Dargaville PA, Gerber A, Johansson S, De Paoli AG, Kamlin OF, Orsini F, et al. Incidence and outcome of CPAP failure in preterm infants. Pediatrics. 2016 Jul;138(1). pii: e20153985.

16. Pillai MS, Sankar MJ, Mani K, Agarwal R, Paul VK, Deorari AK. Clinical prediction score for nasal CPAP failure in pre-term VLBW neonates with early onset respiratory distress. J Trop Pediatr. 2011 Aug;57(4):274–9.

17. Dargaville PA, Aiyappan A, De Paoli AG, Dalton RGB, Kuschel C, Kamlin O, et al. Continuous positive airway pressure failure in preterm infants: incidence, predictors and consequences. Neonatology. 2013;104(1):8–14.

18. De Jaegere A, van der Lee JH, Canté C, van Kaam AH. Early prediction of nasal continuous positive airway pressure failure in preterm infants less than 30 weeks gestation. Acta Paediatr. 2012 Apr;101(4):374–9.

19. Rocha G, Flor-de-Lima F, Proença E, Carvalho C, Quintas C, Martins T, et al. Failure of early nasal continuous positive airway pressure in preterm infants of 26 to 30 weeks gestation. J Perinatol. 2013 Apr;33(4):297–301.

20. Gulzynska E, Szczapa T, Hozejowski R, Borszewska-Kornacka MK, Rutkowska M. Fraction of inspired oxygen as a predictor of CPAP failure in preterm infants with respiratory distress syndrome – a prospective multicenter study. Neonatology. 2019;116(2):171–8.

21. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Te Pas A, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome – 2019 Update. Neonatology. 2019;115(4):432–50.

22. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al. European Consensus Guidelines on the Management of Respiratory Distress Syndrome – 2016 Update. Neonatology. 2017;111(2):107–25.

23. Walsh BK, Daigle B, Di Blasi RM, Restrepo RD. AARC Clinical Practice Guideline. Surfactant replacement therapy: 2013. Respir Care. 2013 Feb;58(2):367–75.

24. Vermont Oxford Network, Manual of operations: https://vtoxford.zendesk.com/hc/en-us/categories/360000861394-Manuals-and-Forms

25. Podgorelec V, Kokol P, Stiglic B, Rozman I. Decision trees: An overview and their use in medicine. J Med Syst. 2002 Oct;26(5):445–63.