Decreasing Chronic Lung Disease Associated with Bubble CPAP Technology: Experience at Five Years

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Abstract

Introduction: Bubble continuous positive airway pressure (bCPAP) is associated with a decreased risk for chronic lung disease (CLD) in preterm neonates. This report examined the effectiveness of adopting bCPAP to reduce respiratory complications and medication usage in a community hospital NICU. Methods: The efficacy of bCPAP was assessed by retrospective examination and comparison of 45 neonates who received bCPAP and 87 neonates who received conventional ventilation only. Data on medication usage were also collected and analyzed. Results: After introduction of the bCPAP protocol, the median number of days on oxygen decreased in the bCPAP group compared with the conventional ventilation only group (median = 33 days, IQR = 7.5–66 vs median = 0, IQR = 0–0; P < 0.001). The exposure to conventional ventilation decreased in the bCPAP group compared with the conventional ventilation only group (median = 18 days, IQR = 5–42.5 vs median = 0, IQR = 0–7; P < 0.001). Postimplementation of bCPAP revealed decreases in CLD from 26 (30%) in the conventional ventilation only group to 2 (4%) in the bCPAP group (P = 0.002); there was also a significant decrease in the use of sedative medications in the bCPAP group compared with the conventional ventilation only group (mean = 5.20 doses, SD = 31.97 vs mean = 1.43, SD = 9.98; P < 0.001). Conclusion: The use of bCPAP results in significant decreases in the use of conventional ventilation, the risk for CLD, and the need for sedative medication. (Pediatr Qual Saf 2020;2:e281; doi: 10.1097/PQS9.0000000000000281; Published online April 10, 2020.)

INTRODUCTION

Chronic lung disease (CLD) continues to be an important cause of long-term morbidity, and a contributing cause of prolonged hospitalization and risk for ventilator-associated pneumonia.1–3 Current literature identifies multiple risks and complications associated with mechanical ventilation, including frequent failure to tolerate early extubation.4,5 Reasons for extubation failure include: upper airway instability, poor respiratory drive, chest wall compliance, alveolar atelectasis, anemia, and ventilation lung damage.6–8

Noninvasive ventilation (NIV), with the early application of nasal continuous positive airway pressure (CPAP), decreases the rate of CLD when compared with institutions where NIV has not been commonly instituted.4,9 CPAP can be delivered using two types of CPAP generators—variable flow and continuous flow systems. Bubble CPAP (bCPAP) has been reported as a safe and cost-effective method for delivering CPAP, both as primary therapy, and as support for the newly extubated preterm infant.10–12 bCPAP utilizes blended gas that is heated and humidified and then delivered through a low-resistance nasal prong. The distal end of the expiratory tubing is submerged underwater; the depth of submersion determines the CPAP pressure generated.13,14

bCPAP was first shown to reduce the need for supplemental oxygen at 28 days of life in an observational study conducted by Avery et al.11 Because of that landmark study, the guidelines for the use of bCPAP have evolved, including recommendations for its use with low birth weight infants.16 More recently, empirical studies have shown that the functional nature of bCPAP decreases the work of breathing, the incidence of intubation, and the need for medication.17,18 Some randomized trials have compared ventilator–derived nasal CPAP with bCPAP in treatment of

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respiratory distress in preterm neonates; however, in an observational study conducted by Khashu et al comparisons were made between 2 groups of less than 32-week babies: those who used ventilator-derived CPAP and those that used bCPAP. Results showed a significant reduction in the use of exogenous surfactant, postnatal steroids, and the duration of mechanical ventilation with the use of bCPAP. Recent literature indicates the use of CPAP over mechanical ventilation decreases the frequency of analgesic or sedative medication use in very low birth weight infants. The purpose of this report is to review our implementation of a system of bCPAP and to evaluate its impact on CLD and sedative medication use in a community hospital NICU.

METHODS

Setting and Patient Sample

This report included 156 infants born in Cottage Children’s Medical Center’s (CCMC) Neonatal Intensive Care Unit in Santa Barbara, Calif., from November 2006 to October 2016. CCMC’s NICU is a 22-bed Level III facility. Infants were included in the study if they received bCPAP, conventional ventilation, or both; and if they were discharged to home or foster care. This project did not require Institutional Review Board approval because it was determined to be quality improvement in nature.

Before November 1, 2011, some exploration of NIV using CPAP had been undertaken, but with limited success, either in avoiding ventilation or in increasing postextubation success. Thus, the initiation of the bCPAP project was carefully timed and prepared. After the development of policies and procedures, identification of clinical champions, and training of the nursing and respiratory staff, we introduced bCPAP on November 1, 2011. Initially we used bCPAP to support larger infants, over 90 days, the gestational age of inclusion was gradually reduced to include all suitable patients.

Intervention

This quality improvement initiative was led by a multidisciplinary team of neonatologists, neonatal nurses, and respiratory therapists who traveled to Columbia Presbyterian’s NICU to study the elements of the successful implementation and maintenance of bCPAP therapy. The core team developed a protocol based on best practice recommendations from Levesque et al. Based on these recommendations, all NICU staff were trained by the core team in guidelines and the technical aspects of bCPAP.

Implementation of the bCPAP guidelines began on November 1, 2011. Training of the staff consisted of small-group sessions with hands-on practice. The core team observed staff initiate and maintain infants on bCPAP while staff learned the nuances of the technique. To ensure compliance with the guidelines, the team used a checklist (Table 1). The team was asked to complete the checklist every 2 hours. During the implementation, the core team maintained high visibility and empowered staff to accomplish changes while offering support and assistance for problem-solving during the transition. The core team members followed up on problems and provided opportunities for staff to clarify issues. The clinical nurse specialist led the team through the quality improvement process and ensured standardization of care. Table 2 outlines a timeline with process-specific details for the implementation of bCPAP.

Measures

Our goal was to evaluate the impact of this practice change on CLD and the use of sedative drugs over a prolonged period. CLD was defined using Vermont Oxford Network Definition 1—the need for supplemental oxygen at 36 weeks postmenstrual age. We collected data on sedative drug use for each patient for the duration of their hospital stay, and comparisons were made between patients who received care during the bCPAP period.

| Date | Time | Time | Time | Time | Time | Time | Time |
|------|------|------|------|------|------|------|------|
| Blended air/oxygen supply is appropriate |      |      |      |      |      |      |      |
| Flow meter at 8L/min |      |      |      |      |      |      |      |
| Humidifier water level is correct |      |      |      |      |      |      |      |
| Excess rainout in tubing is drained |      |      |      |      |      |      |      |
| Nasal Prong size is correct |      |      |      |      |      |      |      |
| Nasal Prongs secure and in place |      |      |      |      |      |      |      |
| PEEP set at 5 cmH2O (unless otherwise ordered) |      |      |      |      |      |      |      |
| Water bubbling continuously |      |      |      |      |      |      |      |
| HOB 30° |      |      |      |      |      |      |      |
| Head position correct |      |      |      |      |      |      |      |
| Hat fits snugly (indicate when removed Q12) |      |      |      |      |      |      |      |
| Corrugated tubing correctly places on hat and not directly touching infants body |      |      |      |      |      |      |      |
| Nasal prongs positioned correctly (not touching the septum, no blanching) |      |      |      |      |      |      |      |
| Septum intact |      |      |      |      |      |      |      |
| Shoulder roll correct size and position for supine/side-lying or prone roll placed for prone |      |      |      |      |      |      |      |
| Pulse oximetry preductal preferred |      |      |      |      |      |      |      |
| Nasal Suctioning PRN |      |      |      |      |      |      |      |
| RN/RT Initials |      |      |      |      |      |      |      |

PEEP, Positive End Expiratory Pressure; HOB, head of bed (elevation); PRN, as needed; RN/RT, Registered Nurse/Respiratory Therapist
Table 2. Timeline for bCPAP Implementation

| Event Description                                                                 | Details                                                                 |
|-----------------------------------------------------------------------------------|------------------------------------------------------------------------|
| CCMC staff travels to Colombia Presbyterian Hospital* in New York for the 22nd Annual Respiratory Care of the Newborn: A Practical Approach Conference | A core multidisciplinary team consisting of neonatologists, neonatal nursing, and respiratory therapy from CCMC traveled to the conference to study and examine the elements of successful implementation and maintenance of bCPAP therapy in October 2011. Educational materials and procedures (based on current best practice literature) in the following areas were created by a core team of NICU staff from August to October 2011: optimal positioning, airway care, feeding considerations, safety considerations, and weaning and discontinuing considerations. An official policy was generated and approved by the Cottage Health system that included; indications, contraindications, possible complications, the equipment needed, procedures, and considerations. |
| CCMC NICU staff training                                                           | All NICU staff were trained in guidelines and technical aspects of bCPAP from October 2011 to December 2011. Training of staff consisted of small-group sessions with hands on practice and included content presentations of the following; theory, rationale, benefits, and clinical practice/implementation of bCPAP. The core team observed staff initiate and maintain infants on bCPAP while staff learned the nuances of the technique. Management guidelines were also created and made available to staff to help guide practice post bCPAP training. These guidelines included tips for troubleshooting (eg, check prong size and placement, ensure airway is clear and positioned midline, and ensure blender is set to appropriate percent of oxygen, absence of bubbling in outlet bottle). |
| bCPAP intervention introduced                                                       | After the development of procedure, policies, identification of clinical champions, and training of NICU clinical staff, bCPAP was introduced on November 1, 2011. |
| Ongoing assessments                                                                | To ensure nursing and respiratory therapy compliance of the bCPAP guidelines, a checklist was created and used by the clinical team. The team completed the checklist every 2 h for 9 mo postimplementation of bCPAP. Table 1 provides details of the checklist used in this study. Vital signs were also taken every 2–3 h as well as continuous monitoring of oxygen saturation. Patient data on the following outcomes were documented for later evaluation postimplementation of bCPAP: rates of CLD, sedative drug use, gender, gestational age, admission weight, length of hospital stay, respiratory distress syndrome, number of days on a ventilator, number of days on oxygen, pneumothorax, PDA, PDAS, necrotizing enterocolitis, intraventricular hemorrhage, intraventricular hemorrhage requiring ventriculoperitoneal shunt, and retinopathy of prematurity. |

* A landmark study by Avery et al found that Colombia Presbyterian Hospital had the best outcomes for low birth weight infants and the lowest incidence of CLD. As a result of this study, CCMCs NICU clinical staff wanted to model and transform Colombia’s elements of successful implementation and maintenance of bCPAP therapy to fit CCMCs community-based hospital setting.

CCMC, Cottage Children’s Medical Center; PDA, Patent Ductus Arteriosus; PDAS, PDA Surgically-repaired.

(31, 2011 to October 31, 2016) to the previous 5-year cohort where bCPAP was not used.

The following clinical outcomes were also measured and compared between the bCPAP and conventional ventilation only groups in this study: gender, gestational age, delivery type (C-section or vaginal), admission weight, length of hospital stay, Respiratory Distress Syndrome, number of days of mechanical ventilation, number of days on oxygen, Pneumothorax, Patent Ductus Arteriosus (PDA), PDA Surgically-repaired (PDAS), Necrotizing Enterocolitis, Intraventricular Hemorrhage (Grades I to IV), Severe Intraventricular Hemorrhage (Grades III or IV), Intraventricular Hemorrhage Requiring Ventriculoperitoneal Shunt (IVHS), and Retinopathy of Prematurity (Grades II or above).

Data Collection and Statistical Analysis

We assessed the effectiveness of bCPAP by retrospective examination and review of charts of patients who received respiratory support that was either by bCPAP or conventional ventilation only. Data were gathered starting 5 years before implementation (November 1, 2006 to October 31, 2011) and 5 years postimplementation of the bCPAP protocol (November 1, 2011 to October 31, 2016). The primary mode of noninvasive ventilation support in the preimplementation period was a high-flow nasal cannula. Data on sedation/analgesia (eg, Ativan, phenobarbital, morphine, or fentanyl) usage were collected and examined.

Statistical analysis was performed using the R Core Team. As this study is exploratory, missing values were treated as a category and were not imputed. For variables containing missing values, the total number of available data points is noted in the table. We defined the baseline covariates as gender, gestational age, delivery type, and admission weight. Gender and delivery type were both balanced, respectively, between the control and the intervention groups ($P > 0.99$), whereas gestational age ($P = 0.009$) and admission weight ($P = 0.02$) were not (Table 3). To account for heterogeneity between the baseline covariates of the control and the intervention groups, we conducted statistical matching using the MatchIt package in R. Specifically, the Matchit function was utilized, and gestational age and admission weight were included as the pretreatment covariates. The nearest neighbor matching method with the Mahalanobis
distance with replacement was chosen when conducting the statistical matching.

Numerical variables were first examined by conducting a Shapiro–Wilk normality test. As none of the numerical data were normally distributed, we chose their median and interquartile range (IQR) as summary statistics. Discrete variables were summarized using absolute and relative frequencies. A 2-sided unpaired student’s t test or 2-sided Wilcoxon rank-sum test was used to test the significance of continuous variables, and a 2-sided chi-square test or 2-sided Fisher’s exact test was used to test the significance of discrete variables.

RESULTS

Before statistical matching, 156 neonates were eligible for this study; their baseline characteristics and outcomes are summarized and compared in Table 3. After matching gestational age and admission weight between the control and intervention groups, we retained 132 neonates in this study for analyses. We report the postimplementation of the bCPAP protocol results as follows.

There were no statistically significant differences in length of stay, the incidence of respiratory distress syndrome, and pneumothorax between the control and the intervention groups (Table 4). The median days on supplemental oxygen for the control group was 33 (IQR = 7.5–66) and 0 (IQR = 0–0) for the intervention group (P < 0.001). There was a median decrease from 18 (IQR = 5–42.5) to 0 (IQR = 0–7) days on a ventilator between the control group and the intervention group (P < 0.001). We observed a decrease in the incidence of chronic lung disease from 26 patients (30%) in the control group to 2 patients (4%) in the intervention group (P = 0.002). Although it did not reach statistical significance at α = 0.05, there was a median decrease from 76 (IQR = 52–104.5) to 66 (IQR = 48–84) days of length of stay between the control and the intervention groups (P = 0.09). PDA and PDAS results favored the intervention group (P = 0.009 and P = 0.008, respectively). We did not report results for IVHS in Tables 3 and 4 because patients in either group did not develop IVHS.

The use of sedatives was investigated and compared between the groups receiving bCPAP or only conventional ventilation. There were markedly more sedative

Table 3. Patient Characteristics and Clinical Outcomes before Statistical Matching

| Clinical Outcomes               | Control (n = 87) | Intervention (n = 69) | p value |
|---------------------------------|------------------|----------------------|---------|
| Male Gender, N (%)             | 48 (55%)         | 38 (55%)             | > 0.99  |
| Gestational Age, median (IQR)  | 27 (25.5 – 29)   | 28 (27 – 30)         | 0.009   |
| Admission Weight g, median (IQR)| 990 (785 – 1200) | 1080 (865 – 1335)    | 0.02    |
| Delivery type; C-section, N (%)| 58, 83 (70%)     | 48, 68 (71%)         | > 0.99  |
| Length of Stay, median (IQR)   | 76 (52 - 104.5)  | 64 (43 – 83)         | 0.019   |
| Respiratory Distress Syndrome, N (%)| 68 (78%)       | 57 (83%)             | 0.62    |
| Days on Ventilator, median (IQR)| 18 (5 – 42.5)   | 0 (0 – 8)            | < 0.001 |
| Days on Oxygen, median (IQR)   | 33 (7.5 – 66)    | 0 (0 – 0)            | < 0.001 |
| Chronic Lung Disease, N (%)    | 26 (30%)         | 4 (5%)               | 0.13    |
| Pneumothorax, N (%)            | 2 (2%)           | 6 (9%)               | 0.14    |
| Patent Ductus Arteriosus (PDA), N (%)| 32 (37%)       | 11 (16%)             | 0.007   |
| PDA, Surgically repaired, N (%)| 15 (17%)         | 0 (0%)               | < 0.001 |
| Necrotizing Enterocolitis, N (%)| 4 (5%)           | 0 (0%)               | 0.13    |
| Intraventricular Hemorrhage (IVH*), N (%)| 17 (20%)      | 6 (9%)               | 0.09    |
| Severe IVH*, N (%)             | 4 (5%)           | 0 (0%)               | 0.13    |
| Retinopathy of Prematurity†, N (%)| 25 (29%)        | 13 (19%)             | 0.21    |

* IVH in our database ranged from 0 to 4; IVH = 0 treated as negative and IVH = 1 – 4 treated as positive; ** IVH = 3 or 4 considered severe IVH; † Retinopathy of prematurity ranged from 0 to 3; 2 and 3 considered positive

Table 4. Patient Characteristics and Clinical Outcomes after Statistical Matching

| Clinical Outcomes               | Control (n = 87) | Intervention (n = 45) | p value |
|---------------------------------|------------------|----------------------|---------|
| Male Gender, N (%)             | 48 (55%)         | 24 (53%)             | 0.97    |
| Gestational Age, median (IQR)  | 27 (25.5 – 29)   | 27 (26 – 30)         | 0.29    |
| Admission Weight g, median (IQR)| 990 (785 – 1200) | 1020 (805 – 1220)    | 0.40    |
| Delivery type; C-section, N (%)| 58, 83 (70%)     | 31, 44 (70%)         | > 0.99  |
| Length of Stay, median (IQR)   | 76 (52 - 104.5)  | 66 (48 - 84)         | 0.09    |
| Respiratory Distress Syndrome, N (%)| 68 (78%)       | 38 (84%)             | 0.53    |
| Days on Ventilator, median (IQR)| 18 (5 – 42.5)   | 0 (0 – 7)            | < 0.001 |
| Days on Oxygen, median (IQR)   | 33 (7.5 – 66)    | 0 (0 – 0)            | < 0.001 |
| Chronic Lung Disease, N (%)    | 26 (30%)         | 2 (4%)               | 0.002   |
| Pneumothorax, N (%)            | 2 (2%)           | 4 (9%)               | 0.19    |
| Patent Ductus Arteriosus (PDA), N (%)| 32 (37%)       | 6 (13%)              | 0.009   |
| PDA, Surgically repaired, N (%)| 15 (17%)         | 0 (0%)               | 0.008   |
| Necrotizing Enterocolitis, N (%)| 4 (5%)           | 0 (0%)               | 0.30    |
| Intraventricular Hemorrhage (IVH*), N (%)| 17 (20%)      | 5 (11%)              | 0.32    |
| Severe IVH*, N (%)             | 4 (5%)           | 0 (0%)               | 0.30    |
| Retinopathy of Prematurity†, N (%)| 25 (29%)        | 10 (22%)             | 0.55    |

* IVH in our database ranged from 0 to 4; IVH = 0 treated as negative and IVH = 1 – 4 treated as positive; ** IVH = 3 or 4 considered severe IVH; † Retinopathy of prematurity ranged from 0 to 3; 2 and 3 considered positive
doses in the conventional ventilation group compared to the bCPAP group (\(P < 0.001\)). Specifically, the average number of sedative doses was 5.20 (SD = 31.97) for the conventional ventilation group and 1.43 (SD = 9.98) for the bCPAP group.

DISCUSSION
We have demonstrated that the successful implementation of bCPAP results in lower incidences of CLD in preterm neonates at our institution. We also observed significant decreases in the use of sedative medications in the bCPAP group compared with the conventional ventilation only group. It has long been recognized that a significant portion of the long-term medical burden carried by premature infants is a consequence of therapy, rather than disease. For example, the variation in the risk of CLD among 8 different centers, as first reported by Avery et al., was striking, and recent reports have raised the concern that sedative medications may have a deleterious effect on the developing brain. Some research suggests negative long-term neurocognitive side effects with the use of sedative drugs in preterm neonates, particularly in very low birth weight infants. Other studies have reported no effect of sedative strategies on infants. For these reasons, developing systems of care that are less invasive and which can allow minimization of the use of potentially harmful medications is highly desirable. bCPAP, when properly administered and carefully monitored, is comfortable and well tolerated by the newborn with acute respiratory failure.

We believe that this is the reason that we have been able to decrease the use of sedative medications substantially compared with the previous period. To date, our findings are the first to show a decrease in sedative medication dosing using bCPAP in a community hospital NICU. These findings may influence standardization and process improvement for other hospitals with similar patient demographics.

Comparative outcome data across California NICUs for CLD (Vermont Oxford Network Definition 1) was prepared by the California Perinatal Quality Care Collaborative (CPQCC) for the specific 5-year intervals before and after the initiation of this bCPAP project. Figures 1, 2A and B demonstrate remarkable improvement in the rate of CLD when compared with all other NICUs in California. Before the initiation of the bCPAP protocol in November 2011, we had attempted NIV in a poorly coordinated way but felt that it had promise. This result is reflected in the lowering CLD rate seen in 2010 (Fig. 1), but it was not until we instituted a system-wide change that we experienced such positive results.

The observation that the incidence of PDA was significantly decreased between the 2 time periods is of interest. Whether this is related to the change in respiratory support modality, or other changes in care, is not clear at this time.

Some limitations of this report include unanticipated difficulty with the use of the bCPAP machine, specifically, the placement of prongs and maintenance of securing devices on the neonates. Through collaborative discussion within the department and communication with clinical experts from Morgan Stanley Children’s Hospital, we undertook

Fig. 1. Changing incidence of CLD following implementation of bCPAP QI project. The circles represent rates of CLD at Cottage CCMC preimplementation and postimplementation of bCPAP from 2003 to 2017. The diamonds show the California Perinatal Quality Care Collaborative (CPQCC) network, the solid line indicates the 95% CI of the O/E CLD ratio. This graph is reprinted with permission from the CPQCC.
improvements in positioning, as well as changes in the frequency of refreshing the securing systems. Other barriers to change, such as time, equipment challenges, the financial cost (e.g., staff training and education), and protocol logistics were overcome to demonstrate and sustain outcomes successfully. To maintain patient safety, we allocated an “introduction period” of 1 year to ensure that we could accomplish definitive practice change. Continued team engagement was crucial to sustain the culture change and a sense of program ownership.

CONCLUDING SUMMARY
We have shown that improved respiratory outcomes and decreased use of sedative drugs for preterm infants can be achieved by the implementation of a bCPAP protocol and using quality improvement methodologies. The essential elements of success for this quality improvement initiative were a collaborative team using standardized practices based on evidence, the implementation of checklists, the frequent reassessment of successes and problems, as well as the use of a core team of clinical experts as resources to the full staff. Physician, nurse, and therapist dedication to the project is essential. We are optimistic that the improved outcomes demonstrated by CCMC’s NICU team are encouraging for process improvement in other community hospital settings.

DISCLOSURE
The authors have no financial interest to declare in relation to the content of this article.

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REFERENCES

1. Martin RJ, Fanaroff AA, Walsh MC. Fanaroff and Martin’s Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant. 10th ed. Philadelphia, Pa.: Elsevier/Saunders.; 2015.

2. Cernada M, Brugada M, Golombek S, et al. Ventilator-associated pneumonia in neonatal patients: an update. Neonatology. 2014;105:98–107.

3. Narendran V, Donovan EF, Hoath SB, et al. Early bubble CPAP and outcomes in ELBW preterm infants. J Perinatol. 2003;23:193–199.

4. Bhatti A, Khan J, Murki S, et al. Nasal Jet-CPAP (variable flow) versus Bubble-CPAP in preterm infants with respiratory distress: an open, randomized controlled trial. J Perinatol. 2015;35:935–940.

5. Davis PG, Henderson-Smart DJ. Nasal continuous positive airways pressure immediately after extubation for preventing morbidity in preterm infants. Cochrane Database Syst Rev. 2003 (2):CD000143.

6. Kori J, Murki S, Gaddam P, et al. Bubble CPAP for respiratory distress syndrome in preterm infants. Indian Pediatr. 2010;47:139–143.

7. Yadav S, Thukral A, Sankar MJ, et al. Bubble vs conventional continuous positive airway pressure for prevention of extubation failure in preterm very low birth weight infants: a pilot study. Indian J Pediatr. 2012;79:1163–1168.

8. Pickerd N, Williams EM, Watkins WJ, et al. Tidal breathing in preterm infants receiving and weaning from continuous positive airway pressure. J Pediatr. 2014;164:1058–1063.e1.

9. Cummings JJ, Polin RA; Committee on Fetus and Newborn American Academy of Pediatrics. Noninvasive respiratory support. Pediatrics. 2016;137:1–11.

10. Merenstein GB, Gardiner SL. Merenstein & Gardiner’s Handbook of Neonatal Intensive Care. 7th ed. St. Louis, Mo.: Mosby Elsevier.; 2011.

11. Tagare A, Kadam S, Vaidya U, et al. Bubble CPAP versus ventilator CPAP in preterm neonates with early onset respiratory distress—a randomized controlled trial. J Trop Pediatr. 2013;59:113–119.

12. Kawasa K, Machen HE, Brown J, et al. Efficacy of a low-cost bubble CPAP system in treatment of respiratory distress in a neonatal ward in Malawi. Malawi Med J. 2016;28:131–137.

13. Gupta S, Donn SM. Continuous positive airway pressure: to bubble or not to bubble? Clin Perinatol. 2016;43:647–659.

14. Welty SE. Continuous positive airway pressure strategies with bubble nasal continuous positive airway pressure: not all bubbling is the same: the Seattle positive airway pressure system. Clin Perinatol. 2016;43:661–671.

15. Avery ME, Tooley WH, Keller JB, et al. Is chronic lung disease in low birth weight infants preventable? A survey of eight centers. Pediatrics. 1987;79:26–30.

16. Aly H, Milner JD, Patel K, et al. Does the experience with the use of nasal continuous positive airway pressure improve over time in extremely low birth weight infants? Pediatrics. 2004;114:697–702.

17. Levesque BM, Kalish LA, LaPierre J, et al. Impact of implementing 5 potentially better respiratory practices on neonatal outcomes and costs. Pediatrics. 2011;128:e218–e226.

18. Bonner KM, Mainous RO. The nursing care of the infant receiving bubble CPAP therapy. Adv Neonatal Care. 2008;8:78–95; quiz 96.

19. Agarwal S, Maria A, Roy MK, et al. A Randomized trial comparing efficacy of bubble and ventilator derived nasal CPAP in very low birth weight neonates with respiratory distress. J Clin Diagn Res. 2016;10:SC09–SC12.

20. Gupta S, Sinha SK, Tin W, et al. A randomized controlled trial of post-extubation bubble continuous positive airway pressure versus infant flow driver continuous positive airway pressure in preterm infants with respiratory distress syndrome. J Pediatr. 2009;154:645–650.

21. Dunn MS, Kaempf J, de Klerk A, et al.; Vermont Oxford Network DRM Study Group. Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. Pediatrics. 2011;128:e1069–e1076.

22. Yagci AC, Vale LA, Haddad LB, et al. Bubble CPAP versus CPAP with variable flow in newborns with respiratory distress: a randomized controlled trial. J Pediatr (Rio J). 2011;87:499–504.

23. Khashi M, Osiovich I, Kozak F, et al. Congenital epiliglottic cyst presenting with severe airway obstruction at birth. J Perinatol. 2006;26:71–72.

24. Mehler K, Oberthuer A, Haertel C, et al.; German Neonatal Network (GNN). Use of analgesic and sedative drugs in VLBW infants in German NICUs from 2003-2010. Eur J Pediatr. 2013;172:1633–1639.

25. Göpel W, Kribs A, Ziegler A, et al.; German Neonatal Network. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. Lancet. 2011;378:1627–1634.

26. Frieden CA, Menchaca RG, Baker MC, et al. Bubble nasal CPAP, early surfactant treatment, and rapid extubation are associated with decreased incidence of bronchopulmonary dysplasia in very-low-birth-weight newborns: efficacy and safety considerations. Respir Care. 2013;58:1134–1142.

27. Isayama T, Chai-Adisaksopho C, McDonald SD. Noninvasive ventilation with vs without early surfactant to prevent chronic lung disease in preterm infants: a systematic review and meta-analysis. JAMA Pediatr. 2015;169:731–739.

28. R: A language and environment for statistical computing [computer program]. Austria R Foundation for Statistical Computing; 2016; Vienna.

29. Ho DE, Kosuke I, King G, Stuart EA. Matching as Nonparametric Preprocessing for Improving Parametric Causal Inference. Annual Meeting; 2004; Chicago IL. https://gking.harvard.edu/files/matchp.pdf.

30. Ferguson SA, Ward WL, Paule MG, et al. A pilot study of preemptive morphine analgesia in preterm neonates: effects on head circumference, social behavior, and response latencies in early childhood. Neurotoxicol Teratol. 2012;34:47–55.

31. McPherson C. Sedation and analgesia in mechanically ventilated preterm neonates: continue standard of care or experiment? J Pediatr Pharmacol Ther. 2012;17:351–364.

32. McPherson C, Grunau RE. Neonatal pain control and neurologic effects of anesthetics and sedatives in preterm infants. Clin Perinatol. 2014;41:209–227.

33. Duerden EG, Guo T, Dodhiba L, et al. Midazolam dose correlates with abnormal hippocampal growth and neurodevelopmental outcome in preterm infants. Ann Neurol. 2016;79:548–559.