Nasal continuous positive airway pressure and outcomes in preterm infants: A retrospective analysis

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OBJECTIVE: The aim of the present retrospective study was to describe the use of nasal continuous positive airway pressure (NCPAP) and the prevalence of bronchopulmonary dysplasia (BPD).
STUDY DESIGN: Data from 1526 neonates with gestational age less than 32 weeks, admitted to Children's and Women's Health Centre of British Columbia (Vancouver, British Columbia) between period 1 (1996 to 2000) and period 2 (2000 to 2004) were analyzed. The use of respiratory therapies and outcomes were retrospectively compared before and after the introduction of a NCPAP approach to respiratory support.
RESULTS: A significant increase in the use of NCPAP was noted between periods 1 and 2 (60% versus 71%), as well as a significant reduction in the use of surfactant (50% versus 41%), postnatal steroids (30% versus 10%) and the need for mechanical ventilation (77% versus 64%). In period 2, there was a significant reduction in the prevalence of BPD at 28 days (33% versus 26%), higher prevalence of severe retinopathy of prematurity (3% versus 6%) and less periventricular leukomalacia (4% versus 2%).
CONCLUSIONS: A significant increase in the use of NCPAP therapy in the neonatal unit has been associated with a decrease in the use of more invasive therapies. The incidence of BPD has decreased if defined as need for supplemental oxygen at 28 days of age, but not when the 36 weeks' postconceptional age criterion was used. NCPAP therapy may decrease the use of more invasive therapies and may improve respiratory outcomes. The impact of this intervention on nonrespiratory outcomes warrants further investigation.

Key words: *Bronchopulmonary dysplasia, CPAP, Neonatology, Premature infants, Retinopathy of prematurity*

La ventilation nasale en pression positive continue et les issues chez les prématurés : Une analyse rétrospective

OBJECTIF : La présente étude rétrospective visait à décrire l'utilisation de la ventilation nasale en pression positive continue (VNPPC) et la prévalence de dysplasie bronchopulmonaire (DBP).
MÉTHODOLOGIE : Les auteurs ont analysé les données de 1 526 nouveau-nés, de moins de 32 semaines d'âge gestationnel, hospitalisés au *Children's and Women's Health Centre* de la Colombie-Britannique pendant la période 1 (1996 à 2000) et la période 2 (2000 à 2004). Ils ont comparé de manière rétrospective le recours à l'inhalothérapie et les issues, avant et après l'implantation de la VNPPC en soutien respiratoire.
RÉSULTATS : Les auteurs ont constaté une augmentation importante du recours à la VNPPC entre la période 1 et la période 2 (60 % par rapport à 71 %), de même qu'une diminution significative du recours aux surfactants (50 % par rapport à 41 %), aux stéroïdes pendant la période postnatale (30 % par rapport à 10 %) et au besoin de ventilation mécanique (77 % par rapport 64 %). Pendant la période 2, ils ont observé une réduction considérable de la prévalence de DBP à 28 jours de vie (33 % par rapport à 26 %), une prévalence plus élevée de grave rétinopathie de la prématurité (3 % par rapport à 6 %) et une diminution de leucomalacie périventriculaire (4 % par rapport à 2 %).
CONCLUSIONS : À l'unité néonatale, une augmentation considérable de la VNPPC s'associe à une diminution du recours aux thérapies plus effractives. L'incidence de DBP a diminué si on la définit comme un besoin d'oxygène d'appoint à 28 jours de vie, mais pas lorsqu'on utilise le critère de 36 semaines d'âge postconceptionnel. La VNPPC peut réduire le recours aux thérapies plus effractives et améliorer les issues respiratoires. Les répercussions de cette intervention sur les issues non respiratoires justifient des recherches plus approfondies.

Over the past decade, major advances in neonatal intensive care have led to increased survival of very low birth weight infants (birth weight 1500 g or less) who were admitted to neonatal intensive care units (NICUs) (1,2). Many studies (3,4) have shown increased rates of major morbidities in those infants who survive, including bronchopulmonary dysplasia (BPD), severe intraventricular hemorrhage and/or necrotizing enterocolitis. BPD remains the major health problem in this population and has been associated with increased risk of mortality and morbidity, such as persistent pulmonary dysfunction, rehospitalization, death during infancy, growth failure and adverse neurodevelopmental outcomes in later childhood (5-11). Lee et al (12) reported a 26% incidence of BPD in very low birth weight infants admitted to 17 NICUs across Canada. More recent data (13) from the National Institute of Child Health and Human Development Neonatal Research Network showed an incidence of 44% in extremely low birth weight

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infants. Several strategies have been attempted to decrease the incidence of BPD, but most of them have met with limited or no success (14).

Since the introduction of continuous positive airway pressure by Gregory et al (15) in 1971, several studies in animals and human infants of early nasal continuous positive airway pressure (NCPAP) have shown promising results in terms of reduction of lung injury, need for mechanical ventilation and incidence of BPD (16-20).

Presently, NCPAP is widely used for a range of neonatal respiratory conditions, including preventing extubation failure and in the management of apnea of prematurity. Some clinicians have advocated increased and early use of NCPAP in the management of respiratory distress syndrome (RDS) in preterm infants, based on the assumption that NCPAP will produce a significant decrease in adverse respiratory outcomes. However, to date, there is little conclusive evidence about this in the published literature. The aim of the present retrospective study was to describe the use of NCPAP and the prevalence of BPD.

METHODS

Sample

The study population was comprised of all inborn infants with gestational ages (GAs) less than 32 weeks, who were admitted to the level 3 NICU at BC Children's Hospital (BCCH), Vancouver, British Columbia, over two time periods: period 1 (June 1996 to May 2000) and period 2 (September 2000 to August 2004). The NICU at BCCH is the largest level 3 NICU in the province of British Columbia.

Respiratory management

No new major technologies were introduced and there were no new changes to clinical practice guidelines during both study periods. The fraction of inspired oxygen was adjusted to maintain an oxygen saturation by pulse oximeter between 88% and 93% in all infants less than 32 weeks' GA treated with supplemental oxygen.

In period 1, infants with RDS were managed with intermittent positive pressure ventilation with bag and mask in the delivery room, early intubation, surfactant administration and intermittent mandatory ventilation. NCPAP was not used in the delivery room and was rarely introduced in the early management of RDS compared with intubation and surfactant administration.

In period 2, delivery room management did not change but the initial management of RDS with NCPAP was encouraged before intubation and mechanical ventilation, or after surfactant administration and a brief period of mechanical ventilation. Underwater 'bubble' NCPAP through short binasal prongs was used immediately after initial stabilization in spontaneously breathing infants. The level of CPAP was kept between 5 cm H_2O and 6 cm H_2O. The decision to introduce this change was made by a multidisciplinary team, and the information was imparted to members of the health care team through daily rounds and academic sessions.

Infants who developed severe and frequent episodes of apnea and bradycardia (more than one episode needing bag and mask ventilation), had a pH lower than 7.25, a partial pressure of CO_2 greater than 60 mmHg and/or required a fraction of inspired oxygen greater than 50% to maintain an oxygen saturation between 88% and 93% were intubated and given exogenous surfactant. These infants were weaned and extubated back to NCPAP as early as possible, based on the clinician's judgement.

Data analysis

Data were obtained from the NICU database at BCCH and retrospectively analyzed.

The demographic and perinatal characteristics of the study population, the use of different respiratory therapies, and respiratory and nonrespiratory outcomes were compared between the two periods.

The population characteristics were compared using *t* tests for continuous variables and through contingency tables and nominal measures of association for nominal variables. The use of respiratory therapies was compared using Pearson's χ^2 test for dichotomous variables and Mann-Whitney U test for nonparametric data. Crude ORs were calculated for respiratory and nonrespiratory outcomes. ORs were also adjusted for demographic and perinatal variables. $P<0.05$ was considered statistically significant. The statistical analysis was conducted with SPSS (SPSS Inc, USA) version 14.0 for Windows (Microsoft Corporation, USA).

RESULTS

During the study period, 1526 neonates who were born at less than 32 weeks' GA were admitted to the NICU at BCCH. Of these, 675 were admitted in period 1 and 851 in period 2.

Demographic and perinatal characteristics did not differ during the two study periods, except for mode of delivery and use of prenatal steroids. In period 2, there was a higher percentage of deliveries by caesarian and fewer infants received prenatal steroid treatment (Table 1).

Table 2 compares the use of respiratory therapies in both study periods. The proportion of infants intubated and mechanically ventilated decreased from period 1 to period 2. The proportion of infants treated with exogenous surfactant also decreased in period 2. The use of NCPAP significantly increased in period 2 compared with period 1. The proportion of infants treated with NCPAP for at least seven days also increased, from 23% in period 1 to 36% in period 2 ($P<0.05$), as well as the number of infants who were treated only with NCPAP (9% versus 19%, $P<0.05$). From period 1 to period 2, the duration of mechanical ventilation and treatment with supplemental oxygen significantly decreased, while the duration of NCPAP therapy increased (Table 2).

The duration of respiratory therapies was also analyzed for each GA group in both periods (Table 3). A significant increase in the median number of days of NCPAP was found in all groups. The median number of days of mechanical

TABLE 1
Demographic and perinatal characteristics of the study population

	Period 1 (n=675)	Period 2 (n=851)
Gestational age, weeks (mean ± SD)	28±2.3	28±2.3
Birth weight, g (mean ± SD)	1195±405	1193±398
Male, n (%)	384 (57)	475 (56)
Multiple births, n (%)	220 (33)	282 (33)
Breech presentation, n (%)	195 (29)	226 (27)
Caesarian delivery, n (%)	348 (52)	491 (58)*
Prenatal steroids†, n (%)	596 (88)	691 (81)*
SGA, n (%)	78 (12)	111 (13)
Apgar score of <4 at 1 min, n (%)	130 (19)	161 (19)
Apgar score of <4 at 5 min, n (%)	22 (3)	23 (3)
PIH, n (%)	86 (13)	116 (13)

**P<0.05; †At least one dose. PIH Pregnancy-induced hypertension; SGA Small for gestational age*

TABLE 2
Use of respiratory therapies

	Period 1 (n=675)	Period 2 (n=851)
Exogenous surfactant, n (%)	340 (50)	347 (41)*
Mechanical ventilation, n (%)	521 (77)	546 (64)*
Median days (IQR)	4 (1–21)	2 (0–10)*
NCPAP, n (%)	408 (60)	603 (71)*
Median days (IQR)	1 (0–5)	3 (0–10)*
Supplemental oxygen, n (%)	586 (87)	658 (77)*
Median days (IQR)	6 (1–38)	4 (1–30)*

**P<0.05. IQR Interquartile range; NCPAP Nasal continuous positive airway pressure*

ventilation decreased in all GA groups, except in the GA group 25 weeks or less. Median days of supplemental oxygen increased in period 2 in the GA group 25 weeks or less (Table 3). The use of postnatal steroids for BPD significantly decreased in period 2 compared with period 1 (10% versus 30%, respectively; P<0.05).

As shown in Table 4, the proportion of infants who required supplemental oxygen at 28 days decreased from period 1 to period 2. This difference persisted after adjustment for demographic and perinatal variables. There were no differences in the percentage of infants requiring supplemental oxygen at 36 weeks' postconceptional age (PCA).

The prevalence of severe (stage 3 or worse) retinopathy of prematurity (ROP) was higher in period 2. The proportion of infants with periventricular leukomalacia (PVL) was lower in period 2. Other nonrespiratory outcomes were similar between both periods (Table 5). Survival to hospital discharge did not change from period 1 to period 2 (90% versus 91%, respectively).

DISCUSSION

Continuous positive airway pressure has been used as part of the initial management of RDS in preterm infants for many years. Over the past 10 years, it has been increasingly used worldwide, partially based on published evidence of effectiveness, but mainly based on clinical experience showing that it is a safe, inexpensive and effective alternative to endotracheal intubation and mechanical ventilation (21).

The mechanism of action of NCPAP is uncertain, but appears to stabilize the upper airway and maintain lung volume, leading to decreased need for intubation, extubation failure and length of mechanical ventilation (22,23). NCPAP has also been associated with decreased BPD in clinical reports (24,25). Van Marter et al (18) have shown intubation and mechanical ventilation to be the single most important predictor of subsequent BPD.

The controversy around the use of NCPAP for the initial management of RDS continues because many of the trials showing beneficial effects were carried out several decades ago in larger infants, before the widespread use of prenatal steroids and exogenous surfactant (26). More recently, different centres have reported encouraging results with the use of this mode of noninvasive respiratory support (16,27-29).

In the present study, we compared outcomes from two periods, before and after a NCPAP approach for the initial management of RDS was introduced, in a large cohort of preterm infants admitted to a single academic tertiary care NICU. The population studied was demographically stable and well defined, except for a higher incidence of deliveries by caesarian, as well as fewer infants who received prenatal steroid treatment in the later period. We found a significant increase in the proportion of infants treated with NCPAP, and a reduction in the use of invasive ventilatory support in period 2. The use of postnatal steroids significantly decreased during period 2, which was likely related to the increasing concerns about adverse effects. This may offset any pulmonary advantages accrued from the application of less invasive respiratory support. Kaempf et al (30) found a nonsignificant trend toward a greater number of infants needing supplemental oxygen at 36 weeks' PCA, in relation to a decrease from 49% to 22% in the use of postnatal dexamethasone in preterm infants born between 501 g and 1250 g.

No significant differences in the incidence of nonrespiratory outcomes, other than ROP and PVL, were found. In period 2, the prevalence of severe ROP was significantly higher, while PVL was lower in comparison with period 1. We do not have a clear explanation for these findings. The policy for oxygen use did not change during the study period. It is possible that NCPAP use was associated with more frequent fluctuations in oxygen saturation that may have favoured the progression of ROP (31-34). However, the criteria for ROP treatment also changed during this period. Other undefined factors may also have affected the results. The lower prevalence of PVL in the later period might be related to the reduced use of invasive ventilatory support. These findings have not been reported in previous studies (16,25,27-29,35), and additional research is needed.

Our study has some limitations. First, it is a retrospective comparison between noncontemporaneous groups; therefore, it is possible that changes in other aspects of management in

TABLE 3
Use of respiratory therapies by gestational age group

	≤25 weeks		26–27 weeks		28–29 weeks		30–31 weeks	
	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2	Period 1	Period 2
Number of infants	110	131	145	146	185	246	235	328
NCPAP, median days (IQR)*	1 (0–6)	7 (0–17)†	5 (1–12)	14 (5–25)†	2 (0–9)	4 (1–9)†	0 (0–2)	1 (0–3)†
Mechanical ventilation, median days (IQR)*	33 (8–44)	36 (6–59)	20 (11–36)	12 (3–28)†	3 (1–11)	2 (0–6)†	0 (0–3)	0 (0–2)†
Supplemental oxygen, median days (IQR)‡	48 (10–69)	57 (6–114)†	38 (14–58)	24 (7–62)	6 (1–23)	6 (1–20)	1 (0–4)	1 (0–4)

**Calculation includes total group of patients; †P<0.05; ‡Includes days on fraction of inspired oxygen greater than 0.21. IQR Interquartile range; NCPAP Nasal continuous positive airway pressure*

TABLE 4
Respiratory outcomes

	Period 1 (n=675)	Period 2 (n=851)	Crude OR (95% CI)	Adjusted* OR (95% CI)
Pneumothorax, n (%)	30 (4)	42 (5)	1.1 (0.7–1.8)	1.4 (0.8–2.3)
Supplemental oxygen at 28 days of age, n (%)	226 (33)	222 (26)	0.7 (0.6–0.9)	0.7 (0.5–0.9)
Supplemental oxygen at 28 days of age or died, n (%)	290 (43)	296 (35)	0.7 (0.6–0.9)	0.7 (0.5–1.0)
Supplemental oxygen at 36 weeks' PCA, n (%)	80 (12)	111 (13)	1.1 (0.8–1.5)	1.2 (0.9–1.7)
Supplemental oxygen at 36 weeks' PCA or died, n (%)	144 (21)	187 (22)	1.0 (0.8–1.3)	1.3 (0.9–1.8)

**Adjusted for gestational age, birth weight, sex, presentation, delivery mode, small for gestational age, Apgar score at 1 min and 5 min, pregnancy-induced hypertension and surfactant. PCA Postconceptional age*

TABLE 5
Nonrespiratory outcomes

	Period 1 (n=675)	Period 2 (n=851)	Crude OR (95% CI)	Adjusted* OR (95% CI)
NEC stage ≥2, n (%)	22 (3)	17 (2)	0.6 (0.3–1.1)	0.5 (0.3–1.1)
Sepsis (any), n (%)	167 (25)	250 (29)	1.2 (1.0–1.5)	1.2 (0.9–1.6)
IVH grade III or IV, n (%)	11 (2)	7 (1)	0.5 (0.2–1.3)	0.5 (0.2–1.4)
PVL, n (%)	27 (4)	17 (2)	0.5 (0.2–0.9)	0.5 (0.3–0.9)
ROP stage ≥3, n (%)	18 (3)	50 (6)	2.1 (1.2–3.7)	2.7 (1.4–5.2)
ROP treated, n (%)	22 (3)	42 (5)	1.5 (0.9–2.6)	1.7 (0.9–3.2)
PDA, n (%)	201 (30)	234 (27)	0.8 (0.7–1.1)	1.2 (0.9–1.5)

**Adjusted for gestational age, birth weight, sex, presentation, delivery mode, small for gestational age, Apgar score at 1 min and 5 min, pregnancy-induced hypertension, surfactant, nasal continuous positive airway pressure days, mechanical ventilation days, supplemental oxygen days. IVH Intraventricular hemorrhage; NEC Necrotizing enterocolitis; PDA Patent ductus arteriosus; PVL Periventricular leukomalacia; ROP Retinopathy of prematurity*

our NICU over the study period could have contributed to the variation in outcomes over time. Second, some important data, such as illness severity scores, were not universally available.

Despite the limitations mentioned above, our study shows in a large cohort of preterm infants, a decrease in the length of mechanical ventilation and oxygen therapy, and in the prevalence of BPD (when defined as need for supplemental oxygen at 28 days) associated with an increased use of NCPAP.

Our findings are in agreement with previous studies (16,27-29,35), which show a reduction in the invasiveness and duration of respiratory support, postnatal steroid use and BPD rates associated with the use of a NCPAP-based approach to respiratory support in preterm infants.

Reducing BPD rates, length of mechanical ventilation and subsequent hospital stay has the potential for major medical, social and economic impact in the delivery of neonatal and subsequent childhood care (16). Therefore, our findings have relevant implications to health care providers and health policy makers.

CONCLUSION

A significant increase in the use of NCPAP therapy in our unit has been associated with a decrease in the use of more invasive therapies. The incidence of BPD has decreased if defined as need for supplemental oxygen at 28 days, but not when the 36 weeks' PCA criterion is used. The incidence of nonrespiratory outcomes, other than severe ROP and PVL, did not change.

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