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ORIGINAL ARTICLE

Nasal continuous positive airway pressure from high flow cannula versus Infant Flow for preterm infants

DM Campbell[1,2], PS Shah[1], V Shah[1] and EN Kelly[1]

[1]Department of Paediatrics, Mt Sinai Hospital, University of Toronto, Toronto, ON, Canada and [2]Department of Paediatrics, St Michael's Hospital, University of Toronto, Toronto, ON, Canada

Objective: To compare the feasibility of continuous positive airway pressure (CPAP) support generated by high flow nasal cannula with conventional CPAP for prevention of reintubation among preterm infants with a birth weight of $\leqslant 1250$ g.

Study Design: Preterm infants were randomized to CPAP generated via high flow cannula or the Infant Flow Nasal CPAP System (*VIASYS*, Conshohocken, PA, USA) at extubation. Primary outcome was incidence of reintubation within 7 days. Secondary outcomes included change in oxygen use and frequency of apnea and bradycardias postextubation.

Results: Forty neonates were randomized. Twelve of 20 infants randomized to high flow cannula CPAP were reintubated compared to three of 20 using Infant Flow ($P = 0.003$). The high flow cannula group had increased oxygen use and more apneas and bradycardias postextubation.

Conclusions: CPAP delivered by high flow nasal cannula failed to maintain extubation status among preterm infants $\leqslant 1250$ g as effectively as Infant Flow CPAP.
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Introduction

Continuous positive airway pressure (CPAP) facilitates extubation by preventing atelectasis, maximizing the functional residual capacity of the lung, and recruiting collapsed alveoli.[1] In preterm infants CPAP decreases the incidence and severity of apneas, reduces the degree of asynchronous breathing, and prevents reintubation following initial extubation.[2,3]

One of the most common forms of CPAP currently used is the Infant Flow system (*VIASYS*) (IF-CPAP). With this device, gas flowing through nasal prongs is facilitated during exhalation via a fluidic-flip design.[4,5] IF-CPAP has been shown to decrease oxygen requirement, improve respiratory effort[6–9] and prevent extubation failure in preterm infants when compared to traditional nasal prong systems and bubble CPAP.[9,10] However, nasal prong CPAP devices have been shown to damage the nares of infants, causing discomfort and rarely, long-term disfigurement.[11,12]

Simple nasal cannula has recently been shown to generate positive end-expiratory pressure (PEEP) in preterm infants if air or oxygen is delivered at a high flow rate (i.e. 1–2 l/min).[13,14] The amount of distending pressure generated by such cannula depends on the size of the cannula, flow rate and size of the infant.[13]

In a recent study, investigators were able to generate a positive distending pressure of 4.5 cm H_2O via simple nasal cannula using a calculated flow rate based on infant's weight. This method of CPAP (high flow CPAP (HF-CPAP)) generated comparable pressure to that delivered by Hudson nasal prong CPAP set to deliver a pressure of 6 cm H_2O.[14] HF-CPAP was also shown to be equally effective compared to the Hudson prong nasal CPAP in the management of apnea of prematurity over a 6 h period.[14] This type of HF-CPAP has the advantage of being easy to administer at a lower cost.

The purpose of this study was to evaluate the feasibility of HF-CPAP in preventing extubation failure of preterm infants with birth weight $\leqslant 1250$ g, compared to IF-CPAP.

Materials and methods

Eligibility

Intubated preterm infants with a birth weight $\leqslant 1250$ g admitted to the Level III neonatal intensive care unit at Mt. Sinai Hospital, Toronto, Canada were eligible for inclusion in this study. Patients were excluded if there were signs and symptoms of upper airway obstruction, or congenital anomalies of the airway.

Randomization and allocation

This study was approved by the Mt Sinai Hospital Research Ethics Board. Informed written consent was obtained from parents before the neonate's first extubation. In our unit, infants are usually extubated to nasal prong CPAP (IF-CPAP) at the time of first

Correspondence: Dr DM Campbell, Department of Paediatrics, St Michael's Hospital, 30 Bond Street, Rm 15-014, Toronto, ON, Canada M5B 1W8.
E-mail: campbelld@smh.toronto.on.ca
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extubation. Time of extubation, ventilatory settings at extubation, and use of caffeine was determined by the medical team. Randomization cards were generated using random number tables and stratified in groups of 10. The randomization cards were sealed in sequentially marked opaque envelopes and opened immediately before extubation. The infants were randomly allocated to either HF-CPAP or IF-CPAP just before extubation.

Procedure

The IF-CPAP circuit used was the Infant Flow system (*VIASYS*©, Conshohocken, PA, USA). Six mm long nasal prongs were available in three sizes (4, 4.5 and 5 mm). The largest prongs that fit easily into the nares were used for each infant. Flow of air/oxygen was adjusted in order to deliver between 5 and 6 cm H_2O of pressure.

The HF-CPAP system consisted of a gas source, air-oxygen blender and a nonheated bubble humidifier delivering air/oxygen via standard nasal cannula (Infant size, Salter Labs, Arvin, CA, USA). HF-CPAP air/oxygen flow through the cannula was adjusted using the following formula as reported by Sreenan *et al*.[14]

$$\text{Flow (l/min)} = 0.92 + 0.68x \; (x = \text{weight in kg})$$

Nasal cannula flow delivered at this rate in very low birth weight preterm infants has been estimated to deliver distending pressure of 4.5 cm H_2O, comparable to that of Hudson nasal CPAP prongs set at 6 cm H_20.[14] In the post-extubation period CPAP was not weaned. Infants were maintained in a proper position to maintain a good seal. Oxygen saturation guidelines for all infants during the study period were identical.

The decision to reintubate an infant was made by the team based on one or more of the following criteria: an uncompensated respiratory acidosis with a pH of <7.25, an oxygen requirement of $>60\%$ to maintain a transcutaneous saturation of $>90\%$, severe apnea (defined as apnea and bradycardia requiring bag and mask ventilation or reintubation for recovery) or frequent apnea (defined as three or more, apneas of any severity in one hour).

Outcome

The primary outcome was success of extubation, defined as remaining extubated for at least 7 days. Secondary outcomes included: change in the amount of oxygen between pre- and postextubation and frequency of apnea and bradycardia events. The definition of apnea was a pause in breathing for >20 s. The definition of bradycardia was heart rate less than 80 beats per minute for 10 s. Nurses' notes were used to record these parameters. Change in oxygen use post-extubation was calculated as the difference between the daily percent FiO_2 post-extubation (over 7 days) and the percent FiO_2 pre-extubation (up to 12 h pre-extubation). Daily percent FiO_2 was estimated by calculating the mean from hourly percent FiO_2 recorded in the chart. Nasal damage was qualitatively assessed by digital photography at 1, 7 and 30 days post-extubation using the following scale: (0) no appreciable damage, (1) mild (erythema of nares), (2) moderate (bleeding of nasal mucosa or nares), (3) severe (deformation of nares, perforation of nasal mucosa). Data regarding: number of days required to come off any form of CPAP, time to reach full feeds, rate of weight gain, frequency of chronic lung disease (need for supplemental oxygen at 36 weeks post-conceptional age), necrotizing enterocolitis, intraventricular hemorrhage, sepsis and retinopathy of prematurity were also collected.

Sample size and statistical analysis

A historical successful extubation rate for preterm infants $\leqslant 1250$ g, observed over 12 months preceding the start of the study, was 70%. In order to demonstrate a difference of 15% in extubation rates between the two strategies, in excess of 400 infants would be required (α of 0.05 and a power of 0.80). A pilot study was therefore undertaken, with 20 patients randomized to each group. Student's *t*-tests were performed for continuous variables and χ^2-test for categorical data. Wilcoxon rank sum tests were used to compare data sets for groups of patients with unequal numbers. Fisher's least significant difference test was used for *post hoc* analysis.

Results

The baseline characteristics were similar for both groups of patients (Table 1). The majority of infants were extubated within 5 days of age in each group ($n = 16$, 80%). Most were extubated from synchronized intermittent mandatory ventilation (HF-CPAP $n = 16$, IF-CPAP $n = 14$) at similar ventilatory settings (Table 1). Other forms of ventilation used before extubation included: pressure support (HF-CPAP $n = 3$, IF-CPAP 2), assist control ventilation (HF-CPAP $n = 0$, IF-CPAP $n = 2$), or high frequency ventilation (HF-CPAP 1, IF-CPAP 2). Mean flow rate used in the HF-CPAP group was 1.6 l/min (range 1.4 to 1.7 l/min). Flow rates used to generate IF-CPAP were not recorded but generally involved flow rates from 6 to 8 l/min. All infants who received caffeine had it administered before extubation.

Twelve of 20 infants, 12 randomized to HF-CPAP required reintubation within 7 days compared to three of 20 infants in the IF-CPAP group (relative risk 2.1, 95% confidence interval 1.3−3.0, $P = 0.003$). Of the 12 infants in the HF-CPAP group who failed extubation, seven were reintubated within 48 h. All infants were reintubated due to severe apnea or increased frequency of apneas.

Secondary outcomes for all infants are reported in Table 2. There were no statistically significant differences noted in the incidence of necrotizing enterocolitis, intraventricular hemorrhage, chronic lung disease, sepsis and retinopathy of prematurity between groups.

Eight of 20 infants extubated to HF-CPAP remained extubated on this form of distending pressure for more than 7 days. This

Table 1 Baseline characteristics of study population

Variables	*HF-CPAP (n = 20)*	*IF-CPAP (n = 20)*	P-*value*
Male:female	11:9	10:10	0.75
Gestational age in weeks	27.4±1.6	27.6±1.9	0.56
Birth weight in grams	1008±157	925±188	0.12
Age at extubation in hours (median and range)	39 (7.5–792)	24 (18–1224)	0.98
Mean airway pressure at time of extubation (cm H_20)	7.7±0.9	7.8±1.3	0.51
Administration of surfactant (*n*)	19	18	1.00
Administration of antenatal steroids (*n*)	18	15	0.41
Administration of caffeine (*n*)	14	9	0.11
% Oxygen use at the time of extubation	21.4±1.1	23.5±5.5	0.13

Abbreviations: IF-CPAP, Infant Flow system (*VIASYS*) continuous positive airway pressure; HF-CPAP, high flow CPAP.
Values expressed as mean±s.d. unless otherwise stated.

Table 2 Primary and secondary outcomes among all randomized infants

Variables	*HF-CPAP (n = 20)*	*IF-CPAP (n = 20)*	P-*value*
Remained extubated at 7 days (*n*)	8	17	0.003*
Change in oxygen use postextubation (%)	4.7±6.4	1.0±2.1	0.025*
Episodes of apnea and bradycardia/day	6±8	2±3	0.045*
Days to reach full feeds	14±6	16±10	0.530
Weight gain postextubation in grams			
7 days	−28±82	−25±64	0.85
14 days	102±125	102±98	0.89
30 days	492±189	521±217	0.57

Abbreviations: IF-CPAP, Infant Flow system (*VIASYS*) continuous positive airway pressure; HF-CPAP, high flow CPAP.
*$P<0.05$; values expressed as mean±s.d. unless otherwise stated.

subgroup of infants also had higher oxygen use post-extubation compared to those who remained extubated on IF-CPAP (2.0±1.9 versus 0.4±1.6, $P = 0.04$). Differences in secondary outcomes were not observed in infants who remained extubated, including time to reach full feeds and weight gain at 7, 14 and 30 days of age.

Nasal damage as assessed by digital photography of stages 1, 2 or 3 was not observed among any infants.

Discussion

Previous studies have demonstrated that high flow nasal cannula can deliver positive distending pressure equivalent to conventional forms of nasal CPAP.[13,14] HF-CPAP has also been shown to be as effective as conventional CPAP in managing apnea of prematurity.[14] As a result of this study the use of high flow nasal cannula as an 'equivalent' form of CPAP has increased. Anecdotal nursing reports also affirmed the early use of HF-CPAP, since it was felt to 'spare' the preterm infants from nasal damage, which was occasionally seen in infants managed with nasal prong CPAP. However, recent reports have demonstrated side effects of high air flow through simple nasal cannula including drying and bleeding of the nasal mucosa as well as airway obstruction.[15,16]

Our findings suggest that HF-CPAP probably should not be used as an equivalent form of CPAP in preterm infants. Compared to IF-CPAP, HF-CPAP was associated with an increase in the number of extubation failures, higher oxygen use, and more apneas and bradycardias. This occurred despite the fact that there was a trend for more infants randomized to the HF-CPAP arm to be on caffeine before extubation. We were unable to detect any nasal damage from either form of CPAP, although this may have been due to 'study effect' in which respiratory therapists and nurses were more careful in monitoring the nares of the infants.

Sreenan *et al*.[14] reported that HF-CPAP was effective in the management of apneas and bradycardias over a 6 h period. The infants studied by Sreenan *et al*.[14] were of higher gestational age compared to this study (30.3 weeks versus 27.5) and also had a higher number of apneas (1–2/6 h) and bradycardias (2–3/6 h). Most of their patients were already established on CPAP, and had therapeutic levels of theophylline. Our findings differ from their report. The reason for this difference may be the outcome studied.

Successful extubation at 7 days was felt to be more clinically relevant outcome and a better overall reflection of CPAP efficacy. Since we were not monitoring pressure delivered by the HF-CPAP device it is possible that we were unable to generate sustained distending pressure for extended periods of time despite replicating Sreenan *et al*'s. technique.

We performed this pilot study to assess the feasibility of this intervention in order to form a basis for a large randomized controlled trial. Perceived advantages of alternate forms of CPAP using simple nasal cannula include ease of administration, possible reduction in nasal damage and increased ability for parents to hold and bond with their infants. We failed to show any benefits with this method of CPAP, and demonstrated that it may be harmful. A *post hoc* power calculation using the observed sample sizes and failure rates, and a type 1 error rate of 5% demonstrates that our study has a statistical power of 87% that the difference in reintubation rates was not due to chance alone.

Limitations of our study include an inability to mask the intervention, small sample size and not monitoring the actual distending pressure generated.

In conclusion, CPAP delivered by high flow nasal cannula failed to maintain extubation status among preterm infants $\leqslant 1250$ g. This form of continuous positive airway pressure is not an effective alternative to conventional nasal continuous positive airway pressure. Its use in other patients, such as older preterm infants, remains to be determined.

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