Comparative evaluation of high-flow nasal cannula and conventional oxygen therapy in paediatric cardiac surgical patients: a randomized controlled trial

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Received 10 February 2014; received in revised form 17 April 2014; accepted 2 May 2014

Abstract

OBJECTIVES: The aim of this study was to compare high-flow nasal cannula (HFNC) and conventional O2 therapy (OT) in paediatric cardiac surgical patients; the primary objective of the study was to evaluate whether HFNC was able to improve PaCO2 elimination in the first 48 h after extubation postoperatively.

METHODS: We conducted a randomized, controlled trial in pediatric cardiac surgical patients under 18 months of age. At the beginning of the weaning of ventilation, patients were randomly assigned to either of the following groups: OT or HFNC. Arterial blood samples were collected before and after extubation at the following time points: 1, 6, 12, 24 and 48 h. The primary outcome was comparison of arterial PaCO2 postextubation; secondary outcomes were PaO2 and PaO2/FiO2 ratio, rate of treatment failure and need of respiratory support, rate of extubation failure, rate of atelectasis, simply to complications and the length of paediatric cardiac intensive care unit stay.

RESULTS: Demographic and clinical variables were comparable in the two groups. Analysis of variance for repeated measures showed that PaCO2 was not significantly different between the HFNC and OT groups (P = 0.5), whereas PaO2 and PaO2/FiO2 were significantly improved in the HFNC group (P = 0.01 and P = 0.001). The rate of reintubation was not different in the two groups (P = 1.0), whereas the need for noninvasive respiratory support was 15% in the OT group and none in the HFNC group (P = 0.008).

CONCLUSIONS: HFNC had no impact on PaCO2 values. The use of HFNC appeared to be safe and improved PaO2 in paediatric cardiac surgical patients.

Keywords: High-flow nasal cannula • Paediatric • Cardiac

INTRODUCTION

High-flow nasal cannula (HFNC) ventilation refers to the delivery of a mixture of air and oxygen via a humidified circuit at very high flows, which exceed the patient’s spontaneous inspiratory demand. HFNC delivers heated and humidified gases and provides some level of continuous positive airway pressure (CPAP), yet the exact amount is unpredictable [1]. Studies in neonates have shown that the amount of CPAP generated depends on several factors, such as the infant’s weight, the delivered flow and the leak around the nasal cannula [1]. A flow-dependent effect of CPAP has been documented in healthy volunteers and in patients with chronic obstructive pulmonary disease treated with HFNC [2]. The use of HFNC has been shown to decrease airway resistance and to flush nasopharyngeal dead space, thus contributing to reduced work of breathing [3, 4], favouring the elimination of CO2 and bronchial secretions [5].

HFNC has been used in several types of respiratory failure in term and preterm infants, children and adults. In many neonatal units, HFNC has been successfully used as an alternative to nasal CPAP. The use of nasal CPAP has previously been shown to reduce the risk of extubation failure among infants, in particular, preterm infants following mechanical ventilation [6]. Several authors have analysed the use of HFNC as a postextubation support in neonates [7, 8]. No data are available in infants after cardiac surgery. Respiratory failure because of fluid accumulation, increased pulmonary vascular resistances, muscular weakness, diaphragmatic fatigue and oedema can be observed in patients after cardiac surgery requiring cardiopulmonary bypass (CPB) [9]. In fact, the postextubation period in this group of patients can be complex, and the use of CPAP or noninvasive ventilation (NIV) can be necessary if conventional O2 therapy (OT) is not enough.

The aim of our study was to investigate whether HFNC postextubation treatment improves CO2 elimination, and our secondary
The primary objective of the study was to evaluate whether HFNC was able to improve PaCO₂ elimination compared with OT at different time points up to 48 h post extubation after paediatric cardiac surgery with CPB.

The secondary objectives of the study were to assess whether HFNC compared with OT was able to improve the following parameters:

(i) PaO₂ and PAO₂/FIO₂ values at different time points up to 48 h post extubation;
(ii) the rate of treatment failure for respiratory or cardiac reasons defined as reported in Table 1 and requirement of postextubation respiratory support;
(iii) the rate of extubation failure;
(iv) the rate of pulmonary atelectasis documented by a radiographer who compared the chest X-ray before extubation with that done 12 h after extubation;
(v) development of nasal progs-related complications defined as nasal ulcers, gastric distension and need for supplemental sedation;
(vi) length of PCICU stay.

**MATERIALS AND METHODS**

Before the beginning of the study, all nurses and medical staff were adequately trained about the use of HFNC by an experienced group of physicians.

**Study design**

A single-centre prospective, un-blinded, randomized, controlled trial was conducted in our 14-bed PCICU. The study was approved by the local Ethics Committee (‘Comitato Etico per la Sperimentazione Clinica’, approval number 313.12) and was registered in the Protocol Registration System (Clinical Trial. Gov. Id: NCT01633801).

**Objectives**

The primary objective of the study was to evaluate whether HFNC was able to improve PaCO₂ values and the PaO₂/FIO₂ ratio, reduction in atelectasis and the need of respiratory support, such as CPAP or NIV, and the reintubation rate in paediatric cardiac surgical patients compared with OT treatments. We also evaluated the complication rate associated with the use of HFNC and the length of paediatric cardiac intensive care unit (PCICU) stay in paediatric cardiac surgical patients.

**Randomization procedure**

The allocation sequence was generated by a computerized random generation programme stratified by two age groups: [1] neonates (surgery before 30 days after birth) and [2] infants (31 days until 18 months after birth). To recruit the same proportion of ages, the number of enrolled neonates was limited to 11 per group (25%), reflecting the institutional rate of neonatal surgery. The children were evaluated for eligibility before surgery and randomized at the beginning of ventilation weaning. Informed consent was obtained from both parents.

**Cannula description**

For HFNC therapy, two types of nasal cannula were selected according to the child’s weight and nare size: (Optiflow) RT329 nasal cannulas (series Bc), which deliver a maximum flow rate of 8 l/min, were applied to infants <4 kg and (Optiflow junior) RT330 (series OPT3XX), which deliver a maximum flow of 20 l/min, were applied to infants >4 kg. Nasal cannulas were 50% smaller than the child’s nares to avoid excessive airway pressures. When an HFNC device was applied, the gas mixture was set at 2 l/kg/min [5]. A pressure limited valve was interposed in the HFNC circuit. As far as conventional OT was concerned, Salter Labs E1601 cannulas delivering a maximum flow rate of 2 l/min were used.

The FiO₂ in the OT group was calculated using Finer’s formula for low-flow oxygen therapy [10, 11]. In all patients, the gas mixture was heated (temperature 36.7°C) and humidified and delivered via a Fisher and Paykel blender.

**Interventions**

All patients received general anaesthesia with sevoflurane induction; maintenance of general anaesthesia varied according to the
anaesthesiologist’s preference. CPB was maintained according to an institutional protocol. At the end of the surgical procedure, children were transferred to the PCICU for postoperative monitoring and ventilator weaning. All patients were ventilated using a volume-guaranteed pressure support (PS) modality with the aim of maintaining tidal volumes in the range 6–8 ml/kg; positive end-expiratory pressure values ranged from 3 to 5 mmHg and they were sedated with a continuous infusion of midazolam (0.05–0.1 mg/kg/h) and morphine (10 µg/kg/h) according to an institutional protocol. Once haemodynamic stability was achieved (heart rate, arterial blood pressure and central venous pressure within normal values) for 12–24 h, sedation with midazolam was discontinued and weaning from mechanical ventilation was started. In this phase, patients were switched to a synchronized intermittent mandatory ventilation–pressure support (SIMV–PS) modality, and they were weaned till a respiratory rate of 10 breaths per minute and a PS in the range of 10–15 cmH2O were achieved. If gas exchanges were within normal ranges by arterial blood gas analysis, a trial of PS ventilation (10–15 cmH2O) was set for 30 min, to be followed by extubation if they were deemed able to breathe spontaneously by the attending anaesthesiologist, the PaCO2 was <55 torr and the peripheral oxygen saturation (SpO2) was above 90% in non-cyanotic infants or above 75% in cyanotic infants. Each study infant was briefly assisted with a facial mask with 100% FiO2. HFNC or OT was placed according to the randomization arm. The attending physician targeted the FiO2 of the administered mixture according to a SaO2 >90% in non-cyanotic infants and a SaO2 >75% in cyanotic infants. In all patients, an orogastric feeding tube was placed and left open for the first 6 h. According to the institutional protocol, children received an infusion of morphine (10 µg/kg/h) until chest drains were removed.

OT and HFNC treatments were considered to have failed if, within 48 h after extubation, an infant, who was receiving maximal respiratory support with the assigned treatment, met two or more of the criteria for cardiac and respiratory failure as defined in Table 1. Infants in whom treatment with OT failed were treated with HFNC, whereas infants on HFNC who failed were treated initially with CPAP and, if this failed, they were treated by NIV. At any point in the study, an urgent intubation and mechanical ventilation was determined by the attending physician in charge.

We collected demographic (age, weight and diagnosis) and baseline data (CPB time, mechanical ventilation length, neonatal age and presence of cyanotic disease). Arterial blood gases were checked and collected at SIMV 10 + PS 10–15 cmH2O at PS 10–15 cmH2O before extubation and 1, 6, 12, 24 and 48 h after extubation (respectively, time points 1, 2, 3, 4, 5, 6 and 7). At the same time points, we recorded heart rate, systolic blood pressure, diastolic blood pressure and respiratory rate. Presence of nasal ulcers, need of supplemental sedation and gastric distension were recorded every 4 h.

The length of mechanical ventilation and PCICU stay were also recorded.

### Statistical analysis

All data were collected on a Microsoft Excel 2007 (Redmond, Washington: Microsoft) database specifically prepared for this study. Continuous data were expressed as mean ± standard deviation (SD) or the median and 25th–75th interquartile range (IQR) and compared by an independent samples t-test or the Mann–Whitney U-test as appropriate for comparison of continuous variables between the two groups (i.e. data at baseline). Two-way analysis of variance (ANOVA) for repeated measures with Bonferroni post hoc analysis was used for analysis of the modification of variables over time in the two groups (i.e. CO2, oxygenation, etc.). Chi square test was used for categorical parameters. The association between PaO2/FiO2 ratio and the use of HFNC was assessed by univariate and multivariate regression analysis. A P-value of less than 0.05 was considered significant.

### Sample size

The study was powered on the primary outcome, based on institutional retrospective data: considering a mean (SD) PaCO2 level, 1 h after extubation, of 45 (10) torr, and a 6-torr PaCO2 difference between the two groups, to achieve an 80% statistical power with an α error of 0.05, the number of patients was calculated to be 49 for each group including five dropouts per arm. Statistical analysis was performed using an SPSS software package (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY, USA).

### RESULTS

One hundred and eight children were eligible, 14 were excluded: 10 because parental consent was denied and 4 because they were extubated before randomization (Fig. 1). A total of 94 patients was enrolled during the study period; however, 89 were analysed. Five patients were excluded from the analysis because of loss of arterial line in the first 6 h (2 in the HFNC group and 3 in the OT group). Forty-six children were enrolled in the OT and 43 in the HFNC group. In the OT group, 10/46 (22%) were cyanotic, whereas 14/43 (33%) were cyanotic in the HFNC group (P = 0.25). Demographic and baseline data at the start of the study were not different between the two groups (Table 2). Heart rate, respiratory rate, blood pressure, arterial pH and arterial lactates were not different between the two groups at the different time points. The two groups were also comparable in terms of diagnosis (Table 3).

PaCO2 values at baseline were not significantly different between the HFNC and OT groups (P = 0.64) and, according to ANOVA for repeated measures, remained similar within the two groups throughout the entire study period (P = 0.5) (Fig. 2A). PaO2
24 h (n = 74, r² = 0.315, P = 0.006; n = 55; r² = 0.407; P = 0.002, respectively) and not by weight, presence of cyanosis and length of CPB and mechanical ventilation.

Treatment failure was 15% (7 patients) in the OT group (6 patients for respiratory and 1 for cardiac reasons) and none in the HFNC group (P = 0.008). All patients with treatment failure required a noninvasive form of respiratory support.

The rate of reintubation was 4.3% (2 patients) in the OT group and 4.6% in the HFNC group (2 patients) (P = 1.0). In the OT group, 1 patient was reintubated because of respiratory failure and 1 because of cardiac failure. In the HFNC group, 1 patient was reintubated due to respiratory failure and 1 because of cardiac failure.

After randomization, one pneumothorax (because of accidental chest tube dislocation) and one chylothorax were observed in each group, whereas three and two pleural effusions were recorded in the HFNC and OT groups, respectively (P = 0.45). After extubation, the rate of atelectasis was 11% in both groups (P = 0.87).

In 2 HFNC patients, the therapy was discontinued because of abdominal distension after 12 and 24 h, respectively: these patients’ data were included in the analysis. No other patients showed HFNC-related complications, such as nasal ulcers or need for supplemental sedation.

The median ventilation time was 1 day in both groups; in the HFNC group, the 25th–75th IQR was 1.5–4 days and in the OT group 1–4 days (P = 0.78). The PCICU median length of stay was 5 days (IQR 3–9 days) in the OT group and 4.5 days (IQR 2–7 days) in the HFNC group (P = 0.56).

**DISCUSSION**

The use of HFNC has recently gained increasing acceptance and popularity in the treatment of several respiratory conditions [12]. HFNCs are currently being applied to patients of all age groups ranging from preterms infants to adults [13]. Several clinical uses for HFNCs have been proposed such as: (i) to prevent extubation failure; (ii) as a primary therapy for respiratory distress syndrome and bronchiolitis; and (iii) to wean from nasal CPAP [13]. Despite the lack of data from randomized trials, HFNCs are increasingly being used in all types of respiratory distress and as an alternative to CPAP and NIV [14, 15] because of the ease of application, tolerability and safety.
A recent prospective, observational study in adults also compared HFNC with conventional oxygen therapy in patients with acute respiratory failure. This small study of 20 patients concluded that the use of the HFNC significantly reduced respiratory rate and improved PaO₂ values [18]. Interestingly, our study showed a beneficial effect of HFNC in a mixed group of cyanotic and acyanotic congenital heart disease patients, showing that the HFNC was probably effective in improving PaO₂ levels of both categories.

A tendency to a lower rate of treatment failure in the HFNC group was also observed in our cohort. Similar results have been shown by other studies. Woodhead et al. [19] in a randomized cross-over study in premature infants comparing HFNC (3.1 ± 0.6 l/min) versus non-humidified high-flow oxygen (1.8 ± 0.4 l/min) observed a significantly lower rate of reintubation in the HFNC group. Holleman-Duray et al. analysed retrospectively 114 premature infants and compared the use of HFNC (4–6 l/min) versus ventilator CPAP (8 cmH₂O); they concluded that infants extubated to HFNC spent significantly fewer days on the ventilator and were extubated from higher ventilator rates [20]. Schibler et al. studied 167 infants with bronchiolitis supported with HFNCs and showed that <5% of infants required intubation [12]. McKiernan et al. [21] showed that HFNC reduced intubation rates in patients with bronchiolitis.

We observed only 2 cases of abdominal distension that required suspension of HFNC therapy. No other major complications were observed. Overall, our study confirms the safety of the use of HFNCs after adequate staff training. In addition, it is important to underline the simplicity of and tolerability to HFNC. This is in line with other studies. In the randomized, controlled trial of Campbell et al., no differences were noted in the incidence of complications or in the reintubation rate between the nasal CPAP and HFNC groups [14]. In preterm infants, HFNC appears to be tolerated more comfortably and to cause less nasal septum trauma [14]. Brink et al. [22] confirmed recently in a prospective observational study the safety of the HFNC in patients with moderate to severe respiratory distress. We used flow rates of 2 l/kg/min as did Brink et al. Previous research has shown that these flows deliver a distending pressure of 4–8 cmH₂O, which could improve the functional residual capacity [22]. A feeding tube was placed orally to avoid mouth closing and abdominal distension soon after extubation.

This study presents some limitations. The period of observation was relatively short and limited to 48 h; however, the study was powered on the PCICU admission time and a relatively minor rate of patients required a PCICU stay longer than 48 h. In addition, we did not examine the possible effects of sedation, although a standard protocol was used in all patients. We were not able to measure nasopharyngeal pressure, and our study was not designed to clarify whether a CPAP effect was present in HFNC patients: as a matter of fact, the study was targeted on clinical variables.

It must be acknowledged that, in our cohort, the distinction between respiratory and cardiac failure patients was difficult to establish.

In conclusion, HFNC is not useful in decreasing PaCO₂ in post-cardiac surgery infants. Conversely, the use of HFNC in paediatric cardiac surgical patients can be considered safe and a better option than OT improve oxygenation and to decrease the need for noninvasive postextubation respiratory support.
ACKNOWLEDGEMENTS

We thank Noemi Bruschini for her support and help with this paper.

Conflict of interest: none declared.

REFERENCES