

Title Page

Title: Efficacy of prophylactic high-flow nasal cannula therapy for postoperative pulmonary complications after pediatric cardiac surgery: a prospective single-arm study

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Abstract

Purpose: This study investigated the incidence of postoperative pulmonary complications (PPC) when high-flow nasal cannula therapy (HFNC) is used prophylactically after pediatric cardiac surgery, and evaluated its efficacy.

Methods: This was a single-arm prospective interventional study that was conducted in a tertiary teaching hospital with eight beds in the pediatric cardiac ICU after approval by the Ethics Committee. One hundred children under the age of 48 months who were scheduled for cardiac surgery for congenital heart disease were recruited. HFNC was used for 24 h after extubation at a 2 L/kg/min flow rate. The primary outcome was the incidence of PPC within 48 h after extubation. PPC was defined as atelectasis and acute respiratory failure meeting certain criteria. We considered prophylactic HFNC as effective if the prevalence of PPC was <10%, based on previous reports of reintubation rates of 6%–9% after pediatric cardiac surgery.

Results: A total of 91 patients were finally included in the analysis. The incidence of PPC within 48 h after extubation was 18.7%, whereas atelectasis was observed in 13.2%, and acute respiratory failure in 8.8%. Reintubation rate within 48 h after extubation was 0%.

Conclusions: We found the incidence of PPC with prophylactic HFNC after planned extubation after pediatric cardiac surgery. However, the incidence was >10%, therefore we could not demonstrate its efficacy in this single-arm study. Further studies are needed to investigate whether the HFNC could be adapted as first-line oxygen therapy after pediatric cardiac surgery.

Manuscript text

Introduction

Postoperative pulmonary complications (PPC) are associated with increased mortality and more extended ICU stays concerning adults [1]. Although there is variation in the definition of PPC, patient background and type of surgery, the incidence has been reported to be 5%–33% for noncardiac surgery [1,2] and 11%–63% for cardiac surgery [3–6].

However, there are no reports on PPC after pediatric cardiac surgery; the postoperative reintubation rate is considered approximately 6%–9% [7,8]. In this line, Gupta et al. reported that the causes of reintubation include acute lung injury [7], therefore prevention of PPC is considered important in pediatric postoperative cardiac surgery.

Noninvasive ventilation (NIV) has been described as a prophylactic method for PPC after pediatric cardiac surgery [9,10], however, potential complications of skin necrosis and pneumothorax may not make this a suitable technique [9,11]. In this regard, the use of a high-flow nasal cannula therapy (HFNC), a respiratory device that delivers warm and humidified gas at a higher flow rate than the patient's inspiratory flow rate [12], is recommended for adults. In comparison to traditional oxygen therapy, using HFNC for 24 h following extubation dramatically reduced the chance of reintubation in adult patients [13]. HFNC increases the functional residual capacity [14], cleans nasopharyngeal dead space [12,15], and reduces airway resistance [16–20]. Moreover, HFNC is assumed to be more comfortable for children than conventional oxygen therapy [21,22], and has been reported to be used in children with bronchiolitis [23–25], interhospital transport [26], and after extubation of neonates [27]. Regarding the efficacy of HFNC after pediatric cardiac surgery, the improvement of the ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen (P/F ratio) [28] and tachypnea improvement effect on acute respiratory failure (ARF) after extubation [29] have been reported; however, there are no reports examining the impact

of HFNC on PPC.

We hypothesized that prophylactic use of HFNC after pediatric cardiac surgery would reduce the incidence of PPC without the occurrence of side effects and could be adapted as first-line oxygen therapy after pediatric cardiac surgery. This study aimed to investigate the efficacy of the prophylactic use of HFNC on the incidence of PPC in children undergoing planned extubation after pediatric cardiac surgery.

Methods

• Study design and setting

This study is a single-arm prospective interventional study in a tertiary teaching hospital that has 865 beds, including eight beds in the pediatric cardiac ICU. We conducted this study in accordance with the principles of the Declaration of Helsinki. This trial was approved by The Institutional Review Board of Okayama University Hospital (study number: 1701-004, approval date: January 17th, 2017, duration of the trial: April 1st, 2017 to March 31, 2018), and registered in the University Hospital Medical Information Network Individual Case Data Repository (registration number: UMIN000025494) before the beginning of the trial and first patient enrollment. The protocol has been published previously [30]. We obtained written informed consent from a parent or guardian of all subjects preoperatively.

• Participants

The inclusion criteria included children under the age of 48 months who were scheduled to undergo corrective cardiac surgery with cardiopulmonary bypass (CPB) for congenital heart disease. Conversely, children who have had palliative surgery for cyanotic heart disease, surgery without CPB, or who have had canceled elective cardiac surgery; the presence of tracheostomy, an unplanned extubation, or a craniofacial abnormality were

excluded; patients could also be excluded from the study according to the physician's clinical judgement.

- Interventions

The study intervention began after the individuals were extubated in the ICU. If the patient was extubated in the operating room, the intervention commenced as soon as the patient was admitted to the ICU. Prophylactic use of the HFNC (Optiflow™ Nasal High-Flow; Fisher & Paykel Healthcare, Tokyo, Japan) will start shortly after extubation, at a flow rate of 2 L/kg/min, at 37°C with a humidifier, and with an adequate fraction of inspiratory oxygen to achieve target oxygen saturation (peripheral oxygen saturation, SpO₂) of ≥94%. The size of the nasal cannula was determined by the patient's weight and nasal size. If intolerance did not develop after extubation, the HFNC was maintained for 24 h.

We lowered the flow rate to 1 L/kg/min if the patient did not tolerate the HFNC at 2 L/kg/min. If intolerance developed at 1 L/kg/min, we lowered the flow rate to <1 L/kg/min or switched the HFNC to traditional oxygen therapy, such as using a facemask and nasal cannula. During the 24-h intervention period, the physician's clinical judgment was used to determine if NIV or reintubation was needed on the basis of clinical symptoms of an increased respiratory rate, poorer gas exchange, or patient intolerance as mentioned below. After the 24-h intervention period, oxygen therapy was not restricted.

The criteria for reintubation were:

1. Worsened ARF (increased respiratory rate, increased partial pressure of arterial carbon dioxide, decreased SpO₂),
2. Decreased the conscious level,
3. Deterioration of cardiovascular functions (cardiac arrest, arrhythmia and heart failure),
4. Clinical judgment of the attending clinicians.

- Data collection

Investigators collected the following data: age in months, body weight, gender, Risk-Adjusted classification for Congenital Heart Surgery (RACHS-1) category [31], cardiac diagnosis, type of surgery, CPB time, operation time, anesthesia time, use of neuromuscular blockade agents during the ICU stay, and duration of mechanical ventilation. The duration of mechanical ventilation is the period of mechanical ventilation from the induction of anesthesia to extubation in the operation room or ICU.

- Outcomes

The primary outcome of this trial was the prevalence of PPC within 48 h after extubation. We defined “PPC” as the combination of atelectasis and ARF after extubation. A radiologist assessed atelectasis using chest radiography on postextubation days 1 and 2. The atelectasis score was used for scoring atelectasis (Table 1) [32]. A score of 3 or higher and exacerbation from before extubation was defined as significant atelectasis. The definition of postextubation ARF is provided in Table 1. This definition comes from the published protocol paper by Shioji et al. [30] on which our study was based and is a modification of the definition from Muñoz-Bonet et al. [33] An investigator diagnosed ARF on postextubation days 1 and 2.

We decided to conclude that prophylactic HFNC is effective if the prevalence of PPC was <10% in our protocol paper. This threshold was decided on the basis of reintubation rates of 6%–9% in previous reports [7,8].

The secondary outcomes were: the reintubation rate within 48 h after extubation, the completion rate of 24-h HFNC, the length of ICU stay, P/F ratio, and HFNC-related adverse events. We defined the “completion rate of 24-h HFNC” as the prevalence of children

who completed 24 h of the prophylactic use of HFNC without any treatment failure. “Treatment failures” were defined as: a flow rate of HFNC of <1 L/kg/min or a change from HFNC to conventional oxygen therapy due to the patient’s intolerance, the need for treatment escalation, or the occurrence of HFNC-related adverse events. “Treatment escalation” is the need for NIV or reintubation.

The P/F ratio was measured during the 24-h HFNC period. We measured this parameter during the period of HFNC at the flow rate of 2 L/kg/min.

“HFNC-related adverse events” were defined as nasal ulcer, pneumothorax, and abdominal distension. The bedside nurse recorded the rate of these events during the 24-h HFNC period.

• Statistical analysis

As mentioned in the outcomes, we set the incidence of PPC $<10\%$ as the threshold for proving the efficacy of prophylactic HFNC based on the reported rate of reintubation after pediatric cardiac surgery (6%–9%) [7,8]. Calculating the sample size from this, we considered that we would need to collect 100 patients to achieve the upper limit of the 95% confidence interval of at least 16%.

The Shapiro–Wilk test was used to assess normality. Continuous data was expressed as medians and their interquartile range (IQR) or as means and their standard deviation (SD). Categorical data was presented as percentages. We compared demographic data for children with PPC and those without PPC if the incidence of PPC is $>10\%$. The Wilcoxon rank–sum test or unpaired t-test was used to compare continuous data. We employed Pearson’s chi-square to compare categorical data. Time-to-event curves were obtained by the Kaplan–Meier method. We considered P-values <0.05 as significant. We used a pairwise elimination method for missing data.

All statistical analyses were performed using statistical software (JMP® 14, SAS Institute, Cary, NC, USA). This software is an upgraded version of the previous JMP12 proposed in the protocol document.

Results

• Patient characteristics

A total of 100 infants were recruited from April 2017 to June 2019. Ninety-one cases were included in the analysis after excluding 9 cases (Figure 1). The characteristics of the patients are shown in Table 2. The median age of the patients was 10 (IQR: 4–18) months, and 10 neonatal cases (11%) were included in the study. The patients' mean weight was 7.1 (SD: 3.0) kg. Regarding the complexity of the surgery, approximately half of the patients were category 3 or higher in the RACHS-1 classification. The median mechanical ventilation time was 15 (IQR: 4–46) h. Three patients were extubated in the operating room, 41.8% of the patients within 6 h postoperatively, however, four patients were under ventilation for >1 week postoperatively. Thirty-one children (34.1%) received continuous muscle relaxants during postoperative ventilation via endotracheal tube as a part of sedation.

• Primary outcome

The results are shown in Table 3. The incidence of PPC within 48 h after extubation was 18.7% (17 out of 91 patients). Among them, atelectasis was seen in 13.2% of the cases, and ARF occurred in 8.8% of the cases. The Kaplan–Meier curve of PPC-free days is shown in Figure 2.

• Secondary outcomes

There were no reintubation cases within 48 h after extubation. One patient was

reintubated within 56 h after extubation due to circulatory instability caused by atrial tachycardia.

Although the flow rate was lowered to 1 L/kg/min in two cases for agitation, the accomplishment rate of 24-h HFNC was 100%. Four cases were omitted because HFNC was stopped or the flow rate modified due to a protocol violation without the patient's intolerance or the incidence of HFNC-related adverse effects (Figure 1).

The median length of stay in the ICU was 5 (IQR: 4–9) days. Table 3 and Figure 3 demonstrate the trend of the P/F ratio throughout time. In terms of HFNC-related adverse events, one patient experienced pneumothorax, which was diagnosed by the cardiac surgeon as air retraction from the thoracic drain and was ruled out as being caused by HFNC.

• Subgroup analysis

We performed a subgroup analysis between the PPC group and the non-PPC group (Table 2, 3). There were no significant differences in patient background.

The trend of P/F ratio in both groups is shown in Figure 3. The P/F ratio was lower in the PPC group with a significant difference except 6–12 h after extubation. This tendency was more pronounced at 0–6 h after extubation. Nevertheless, improvement was observed after that.

The median ICU stay in the PPC group was 7 (IQR: 5–9.5) days, compared with 5 (IQR: 3–9) days in the non-PPC group, but the difference was not significant.

Discussion

This is the first single-arm interventional trial to investigate the incidence of PPC following pediatric cardiac surgery and the efficacy of prophylactic HFNC. We were unable to conclude from this study that using preventive HFNC following pediatric cardiac surgery is

useful in preventing PPC.

We think that this is mainly due to the predetermined PPC incidence threshold of 10%. The definition of PPC has not been established in either adults or children. Previous studies have defined PPC as the development of at least one of the following within 7–30 days postoperatively: atelectasis, respiratory failure, pleural effusion, pneumothorax, bronchospasm, respiratory infection, aspiration pneumonia, or acute respiratory distress syndrome [1,2,34]. In this study, atelectasis and ARF were selected as PPC because they are the most common pulmonary complications in children after pediatric cardiac surgery. Pleural effusion and pneumothorax were excluded from the definition of PPC because they are more likely to be influenced by the surgical technique than by the method of postoperative respiratory support. As mentioned earlier, HFNC has beneficial effects such as providing accurate fractional oxygenation and gentle, positive airway pressure, cleaning the nasopharyngeal dead space, and reducing airway resistance [12,15–20], and it was hypothesized that the use of prophylactic HFNC might reduce the incidence of PPC after extubation following pediatric cardiac surgery. However, as there was no control group in this study, it was necessary to establish a threshold to examine this hypothesis. We set the incidence of PPC at <10% as a threshold for the effectiveness of prophylactic HFNC based on previous reports of 6%–9% reintubation rates after pediatric cardiac surgery [7,8] because there were no reports on the incidence of PPC after pediatric cardiac surgery at the time of protocol development. However, a recent prospective observational study assessing the usefulness of lung ultrasonography for early diagnosis of PPC after juvenile heart surgery found a 34% incidence of PPC [35]. Furthermore, as the rate of atelectasis in adult patients following noncardiac surgery (17%) is 10 times higher than the rate of reintubation (1.7%) [1], the rate of PPC is likely to be higher. In fact, in this study, the incidence of PPC was 18.7%, but the rate of reintubation within 48 h after extubation was 0%. For these reasons, we think

that the threshold of 10% set to study the effectiveness of prophylactic HFNC was too low. We believe that further studies are needed to investigate whether prophylactic HFNC is effective for PPC after pediatric cardiac surgery.

In pediatric cardiac surgery, children with low respiratory reserve capacity, especially neonates and infants, are considered to be at higher risk of developing PPC due to the effects of pulmonary compliance reduction caused by increased vascular permeability and decreased surfactant function associated with CPB, as well as pulmonary mechanical changes related to general anesthesia and surgical techniques, and cooling for myocardial protection [36–40]. Pulmonary complications are associated with higher morbidity and mortality, higher healthcare costs, and more extended hospital stays [41]. Given the potential for pulmonary complications, optimizing perioperative respiratory care is critical to improving outcomes after pediatric cardiac surgery.

The efficacy of NIV as a prophylactic respiratory support method after pediatric cardiac surgery has been reported previously [9,10]. Gupta et al. retrospectively studied the efficacy of prophylactic NIV in critically ill cardiac patients between 1 day and 18 years of age who received NIV in a pediatric cardiovascular ICU and found that prophylactic NIV shortened hospital stay. Still, complications included nasolacrimal skin necrosis in 8% and pneumothorax in 4% [9]. In addition, in a multicenter randomized controlled trial comparing nasal continuous positive airway pressure (nCPAP) and HFNC in children with acute bronchiolitis, it was reported that the occurrence of pneumothorax was 0% in both groups, but skin lesions occurred in 8.5% of the nCPAP group and 2.8% of the HFNC group [11]. In this study, pneumothorax was observed in one patient, however it was diagnosed by the cardiac surgeon as air entrainment from the drain and not a complication due to HFNC, and the incidence of skin lesions was 0%. Furthermore, the achievement rate of 24-h HFNC was 100% against the report of intolerance in 20% of infants who received nCPAP [21]. Although

no reports have compared NIV and HFNC after pediatric cardiac surgery, and this is a single-arm study, we speculate that HFNC may be safer and more comfortable than NIV.

This study has a number of limitations, which are listed below. First, we used the reintubation rate as a threshold for analyzing the efficacy of HFNC because it was a single-arm study and we could not locate any publications on the incidence of PPC after pediatric cardiac surgery, and we also used the reintubation rate rather than the PPC incidence rate in calculating the sample size. Second, as the definition of PPC is unclear, the current study had its own definition of PPC, referring to the previous findings. Third, the monitoring period was only 48 h following extubation. Fourth, the subject of this study was limited to a single center, children within 48 months, and cardiac surgery using CPB. Finally, the evaluation of P/F ratio became complicated because we did not consider the presence or absence of fenestration in Fontan or residual Atrial Septal Defect in right ventricular dysfunction.

Conclusions

To summarize, we discovered the incidence of PPC when preventive HFNC was used following scheduled extubation for pediatric cardiac surgery, but we could not conclude its efficacy in this single-arm trial. More research is needed to determine if the HFNC could be used as a first-line oxygen therapy for children who have undergone heart surgery.

Acknowledgments

Not applicable.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

Authors' contributions

Tatsuhiko Shimizu performed the statistical analyses and wrote the manuscript. Tomoyuki Kanazawa conducted the research process, performed data collection, and managed the research activity. Naohiro Shioji designed the study, conducted the research process, and performed data collection. Takanobu Sakura, Kazuyoshi Shimizu, Ryuichiro Fukuhara, Takayoshi Shinya and Tatsuo Iwasaki performed the investigation process. Hiroshi Morimatsu supervised the research activity. All authors revised the manuscript critically and approved the final version of the manuscript to be published.

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Figure Legends

Figure 1 Patient flow diagram in this study.

Of the 100 patients who were recruited, 3 were excluded owing to nonfulfillment of the indication criteria, and an additional 6 were excluded owing to protocol violations or other reasons; thus, the final count of patients available for analysis was 91.

HFNC: high-flow nasal cannula.

Figure 2 Kaplan–Meier curve on postoperative pulmonary complication-free days.

The percentage of postoperative pulmonary complication-free patients decreased to 91.2% on the day of extubation and 82.4% on the day after extubation.

PPC: postoperative pulmonary complication.

Figure 3 Changes in the P/F ratio over time for all cases and subgroup analysis.

The distribution of P/F ratios for all cases on the left, the group without PCC in the center, and the group with PCC on the right for the following timings: pre-extubation, 0–6 h postextubation, 6–12 h postextubation, 12–18 h postextubation, and 18–24 h postextubation, respectively.

P/F ratio: the ratio of the partial pressure of arterial oxygen to the inspiratory oxygen fraction;

PPC: postoperative pulmonary complication.

Figures

Figure 1

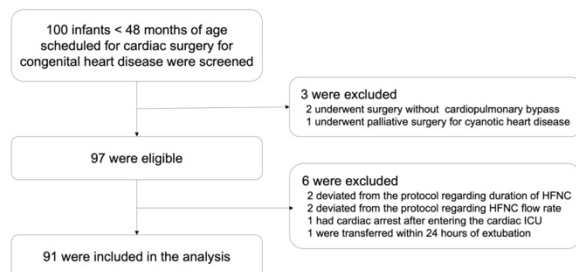


Figure 2

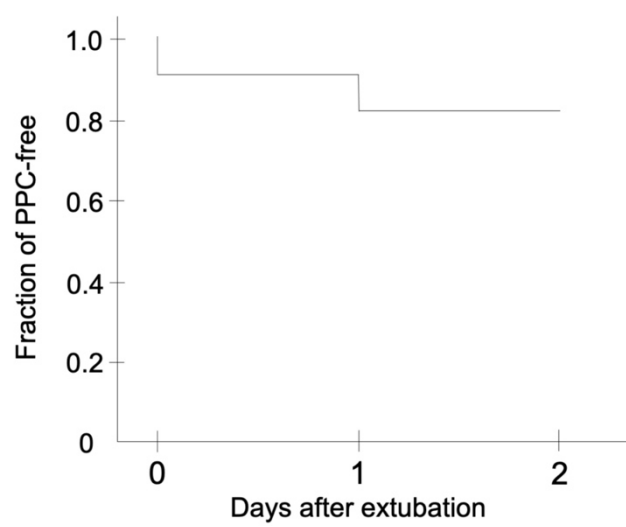


Figure 3

