

Acta Med. Okayama, 2018
Vol. 72, No. 2, pp. 193-196

Copyright©2018 by Okayama University Medical School.

Acta Medica
Okayama

<http://escholarship.lib.okayama-u.ac.jp/amo/>

Clinical Study Protocol

Incidence of Pulmonary Complications with the Prophylactic Use of High-flow Nasal Cannula after Pediatric Cardiac Surgery: Prophylactic HFNC Study Protocol

Naohiro Shioji, Tomoyuki Kanazawa*, Tatsuo Iwasaki, Kazuyoshi Shimizu, Tomohiko Suemori, Hirokazu Kawase, Satoshi Kimura, Yasutoshi Kuroe, and Hiroshi Morimatsu

Department of Anesthesiology and Resuscitology, Okayama University Hospital, Okayama 700-8558, Japan

We will investigate the incidence of postoperative pulmonary complications (PPCs) with the prophylactic use of a high-flow nasal cannula (HFNC) after pediatric cardiac surgery. Children <48 months old with congenital heart disease for whom cardiac surgery is planned will be included. The HFNC procedure will be commenced just after extubation, at a flow rate of 2 L/kg/min with adequate oxygen concentration to achieve target oxygen saturation $\geq 94\%$. This study will reveal the prevalence of PPCs after pediatric cardiac surgery with the prophylactic use of HFNC.

Key words: high-flow nasal cannula, postoperative pulmonary complications, pediatric cardiac surgery, congenital heart disease

Postoperative pulmonary complications (PPCs) are associated with high mortality and long intensive care unit (ICU) stays in adults [1]. The PPC incidence in two studies of adult patients ranges from 5% to 33%, depending on the definition of PPCs, the patients' characteristics, and the types of surgery [1,2]. The prevention of PPCs is important in children as well as adults. The rate of reintubation after pediatric cardiac surgery has been reported to be approx. 6-9% [3,4]. Little is known about the incidence of PPCs in children after cardiac surgery.

Some interventions to prevent PPCs are perioperatively provided in adults. These include lung protective mechanical ventilation, intermittent positive pressure breathing, deep-breathing exercises, intensive spirometry, and chest physiotherapy. Among these interventions, the intraoperative strategy of lung protective

mechanical ventilation with a low tidal volume, high positive end expiratory pressure, and recruitment maneuvers has been the only preventive method to show evidence of reducing the incidence of PPCs [5]. However, applying lung protective mechanical ventilation for children undergoing cardiac surgery may be deleterious because of pulmonary hypertension, single ventricle physiology, and low cardiac output syndrome.

High-flow nasal cannula (HFNC) is a respiratory support device that can deliver heated and humidified gas at a higher rate than the patient's inspiratory flow rate [6]. The 24-h use of HFNC significantly reduced the risk of reintubation in extubated adult patients compared to conventional oxygen therapy [7]. HFNC have been used for children with bronchiolitis, in the interhospital transport of critically ill children, and in the postextubation period in neonates [8-11]. The use of HFNC has beneficial effects compared to conventional oxygen ther-

Received June 15, 2017; accepted October 24, 2017.

*Corresponding author. Phone: +81-86-235-7778; Fax: +81-86-235-6984
E-mail: tyskanazawa@gmail.com (T. Kanazawa)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

apy in that it provides precise fractional oxygen delivery and mild positive airway pressure, flushes the nasopharyngeal dead space, and reduces airway resistance [12-15]. Moreover, HFNC may be more comfortable for children than conventional oxygen therapy [16].

We therefore speculated that the use of HFNC could be a first-line oxygen therapy following extubation after pediatric cardiac surgery for the purpose of respiratory support. We have planned the present study to determine the incidence of PPCs with the prophylactic application of HFNC in extubated children who are scheduled to undergo pediatric cardiac surgery. We hypothesize that the prophylactic use of HFNC will be associated with a low incidence of PPCs and that this therapy will be applicable for first-line oxygen therapy after pediatric cardiac surgery.

Methods

Design and study setting. This study is a single-arm prospective interventional study. We will conduct the study in a tertiary teaching hospital that has 865 beds including 8 beds in the pediatric cardiac ICU. This trial is registered in the University Hospital Medical Information Network Individual Case Data Repository (UMIN000025494).

Ethics. The Institutional Review Board of Okayama University Hospital approved this study (no. 1701-004). We will obtain written informed consent from a parent or guardian of all of the subjects preoperatively.

Eligibility criteria. The inclusion criterion is: a child <48 months old for whom cardiac surgery for congenital heart disease is planned. The exclusion criteria are: children who have undergone palliative surgery for cyanotic heart disease, who have undergone surgery without cardiopulmonary bypass, or whose elective cardiac surgery has been canceled; the presence of a tracheostomy, an unplanned extubation, or a craniofacial abnormality; or the clinical judgment of the physician.

Study interventions. The study intervention protocol is illustrated in Fig. 1. The study intervention will start after extubation in subjects in the ICU. If the subject was extubated in the operation room, the intervention will start just after the subject arrives at the ICU. The use of the high-flow nasal cannula (HFNC) (Optiflow™ Nasal High Flow; Fisher & Paykel Healthcare, Tokyo, Japan) will be prophylactically commenced just 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 (SpO_2) $\geq 94\%$. The nasal cannula size will be selected based on the patient's weight and nasal size. The use of the HFNC will be continued for 24 h after extubation if intolerance does not occur.

If the patient is not tolerant to the HFNC with a flow rate of 2 L/kg/min, we will reduce the flow rate to 1 L/kg/min. If intolerance occurs at the flow rate of 1 L/kg/min, we will reduce the flow rate to <1 L/kg/min or change the HFNC to conventional oxygen therapy such as therapy using a facemask and a nasal cannula. The selection criteria for noninvasive ventilation (NIV) or reintubation during the 24-h intervention period are the physician's clinical judgment based on the observation of clinical signs of an increased respiratory rate (RR), worsening gas exchange, or patient intolerance. There will be no limitation of oxygen therapy after the 24-h intervention period.

Data collection. Investigators will collect the following data: age in months, body weight, gender, Risk Adjusted classification for Congenital Heart Surgery (RACHS-1) category [17], cardiac diagnosis, type of surgery, cardiopulmonary bypass time, operation time, anesthesia time, use of neuromuscular blockade agents during the ICU stay, and duration of mechanical ventilation. Duration of mechanical ventilation is defined as the period on mechanical ventilation from the induction of anesthesia to extubation in the operation room or ICU.

Endpoints. This study's primary outcome is the prevalence of PPCs (as defined below) within 48 h

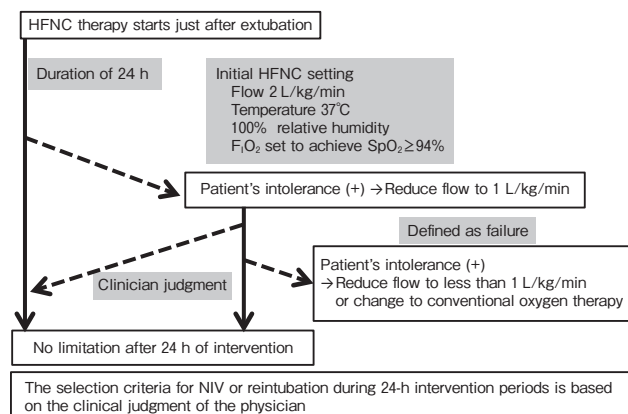


Fig. 1 Study intervention protocol. HFNC, high-flow nasal cannula; F_iO_2 , inspiratory oxygen fraction SpO_2 , oxygen saturation of a peripheral artery; NIV, noninvasive ventilation

after extubation. The secondary outcomes are the reintubation rate within 48 h after extubation, the rate of completion of 24-h HFNC, the length of ICU stay, the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (P/F ratio), and HFNC-related adverse events.

Definitions of endpoints. We define ‘PPCs’ as the combination of atelectasis and acute respiratory failure (ARF) after extubation. A radiologist will assess atelectasis by chest radiography on postextubation days 1 and 2. The definition of postextubation ARF is provided in Table 1. This definition is a modification of a previous definition [18]. An investigator will diagnose ARF on postextubation days 1 and 2. We will conclude that prophylactic HFNC is effective if the prevalence of PPCs is < 10%. This threshold was decided on the basis on reintubation rates of 6-9% in previous reports [3,4]. The criteria for reintubation are: (1) worsened ARF (increased RR, increased partial pressure of arterial carbon dioxide, decreased SpO₂), (2) decreased conscious level, (3) deterioration of cardiovascular functions (cardiac arrest, arrhythmia and heart failure), and (4) clinical judgment of the attending clinicians.

We define the ‘completion rate of 24-h HFNC’ as the prevalence of children who complete 24 h of the prophylactic use of HFNC without any treatment failure. ‘Treatment failures’ are 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

Table 1 Definition of postextubation acute respiratory failure

1. Increased RR for the patient’s age + the use of accessory respiratory muscle RR > 50 breaths per min (< 1 year old) RR > 40 breaths per min (1–4 years old)
2. Hypoxemic acute respiratory failure (type 1) PaO ₂ < 60 mmHg or SaO ₂ < 90% (with F _I O ₂ > 0.5)
3. Hypercapnic acute respiratory failure (type 2) pH < 7.35 with PaCO ₂ > 50 mmHg
4. Mixed form of acute respiratory failure: both criteria 2 and 3

‘Postextubation acute respiratory failure’ is defined by at least one of the criteria 1–4.

F_IO₂, inspiratory oxygen fraction; PaCO₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen; RR, respiratory rate; SaO₂, oxygen saturation.

the need for NIV or reintubation. NIV is initiated according to the clinical judgment of the physician based on clinical signs of increased RR, worsening gas exchange or patient intolerance.

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

‘HFNC-related adverse events’ are defined as nasal ulcer, pneumothorax, and abdominal distension. The bedside nurse will record the rate of these events during the 24-h HFNC period.

Statistical consideration. The prophylactic use of HFNC might have the potential to reduce the incidence of PPCs following extubation after pediatric cardiac surgery. To investigate this possibility, we will set the incidence of PPCs at < 10% as a threshold of the effectiveness of prophylactic HFNC on the basis of the reported reintubation rates in children who underwent cardiac surgery (6-9%) [3,4]. We estimated that a sample size of 100 patients would be required to set the upper limit of the 95% confidence interval to > 16%. An interim analysis is planned after the collection of data from 50 children.

The Shapiro-Wilk test will be used to assess normality. Continuous data will be expressed as medians and their interquartile range (IQR) or as means and their standard deviation (SD). Categorical data will be presented as percentages. We will compare demographic data for children with PPCs and those without PPCs if the incidence of PPCs is > 10%. The Wilcoxon rank sum test or unpaired-*t*-test will be used to compare continuous data. Pearson’s chi-square test will be used to compare categorical data. Time-to-event curves will be obtained by the Kaplan-Meier method. *P*-values < 0.05 will be considered significant. All statistical analyses will be performed using statistical software (JMP® 12, SAS Institute, Cary, NC, USA).

Discussion

This study is the first single-arm prospective interventional study aiming to determine the prevalence of PPCs following extubation after pediatric cardiac surgery under the condition of the prophylactic use of HFNC.

The definition of PPCs has not been established in adults or children. In previous studies, PPCs were defined as the development of at least one of the following within 7-30 postoperative days: atelectasis, respira-

tory failure, pleural effusion, pneumothorax, bronchospasm, respiratory infection, aspiration pneumonitis, and acute respiratory distress syndrome [1, 2, 19]. We have selected atelectasis and ARF as PPCs in this study because they are the most common pulmonary complications in children after pediatric cardiac surgery. We exclude pleural effusion and pneumothorax from the definition of PPCs because the incidences of these complications are more likely to be affected by the surgical procedure during cardiac surgery than the method of postoperative respiratory support.

As noted above, we speculate that the prophylactic use of HFNC might have the potential to reduce the incidence of PPCs following extubation after pediatric cardiac surgery. We must set a threshold to investigate this hypothesis because this study has no control group. We finally decided that the prevalence of PPCs should be set to < 10% as a threshold of the effectiveness of prophylactic HFNC on the basis of data including the reintubation rate in children undergoing cardiac surgery in previous studies and on the basis of the prevalence of PPCs in adults (due to the lack of data for PPCs in children). As we noted earlier, the rate of reintubation after pediatric cardiac surgery is approx. 6-9% [3,4]. Among several surgical procedures, cardiac surgery has the highest rate of PPCs in adult patients (39%), much higher than the rate of 5% in general cohorts [4]. Another study showed that the rate of atelectasis (17%) was ten times higher than the reintubation rate (1.7%) in adult patients following noncardiothoracic surgery [1]. We thus consider the 10% threshold reasonable for the incidence of PPCs in this study.

Trial status. Enrollment in the study was initiated on April 1, 2017.

Acknowledgments. We thank Professor Shiro Hinotsu at the Center for the Innovative Clinical Medicine in Okayama University Hospital for his assistance with the protocol design.

References

- Fernandez-Bustamante A, Frendl G, Sprung J, Kor DJ, Subramaniam B, Martinez Ruiz R, Lee JW, Henderson WG, Moss A, Mehdiratta N, Colwell MM, Bartels K, Kolodzie K, Giquel J and Vidal Melo MF: Postoperative Pulmonary Complications, Early Mortality, and Hospital Stay Following Noncardiothoracic Surgery: A Multicenter Study by the Perioperative Research Network Investigators. *JAMA Surg* (2017) 52: 157-166.
- Canet J, Gallart L, Gomar C, Paluzie G, Vallès J, Castillo J, Sabaté S, Mazo V, Briones Z and Sanchis J; ARISCAT Group: Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* (2010) 113: 1338-1350.
- Gupta P, Rettiganti M, Gossett JM, Yeh JC, Jeffries HE, Rice TB and Wetzel RC: Risk factors for mechanical ventilation and reintubation after pediatric heart surgery. *J Thorac Cardiovasc Surg* (2016) 151: 451-458.
- Gaies M, Tabbutt S, Schwartz SM, Bird GL, Alten JA, Shekerdemian LS, Klugman D, Thiagarajan RR, Gaynor JW, Jacobs JP, Nicolson SC, Donohue JE, Yu S, Pasquali SK and Cooper DS: Clinical Epidemiology of Extubation Failure in the Pediatric Cardiac ICU: A Report From the Pediatric Cardiac Critical Care Consortium. *Pediatr Crit Care Med* (2015) 169: 837-845.
- Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B and Jaber S; IMPROVE Study Group: A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med* (2013) 369: 428-437.
- Lee JH, Rehder KJ, Williford L, Cheifetz IM and Turner DA: Use of high flow nasal cannula in critically ill infants, children, and adults: a critical review of the literature. *Intensive Care Med* (2013) 39: 247-257.
- Hernández G, Vaquero C, González P, Subira C, Frutos-Vivar F, Rialp G, Laborda C, Colinas L, Cuenca R and Fernández R: Effect of Postextubation High-Flow Nasal Cannula vs Conventional Oxygen Therapy on Reintubation in Low-Risk Patients: A Randomized Clinical Trial. *JAMA* (2016) 13: 1354-1361.
- Hough JL, Pham TM and Schibler A: Physiologic effect of high-flow nasal cannula in infants with bronchiolitis. *Pediatr Crit Care Med* (2014) 15: 214-219.
- Schlapbach LJ, Schaefer J, Brady AM, Mayfield S and Schibler A: High-flow nasal cannula (HFNC) support in interhospital transport of critically ill children. *Intensive Care Med* (2014) 40: 592-599.
- Manley BJ, Owen LS, Doyle LW, Andersen CC, Cartwright DW, Pritchard MA, Donath SM and Davis PG: High-flow nasal cannulae in very preterm infants after extubation. *N Engl J Med* (2013) 369: 1425-1433.
- Turnham H, Agbeko RS, Furness J, Pappachan J, Sutcliffe AG and Ramnarayan P: Non-invasive respiratory support for infants with bronchiolitis: a national survey of practice. *BMC Pediatr* (2017) 17: 20.
- Dewan NA and Bell CW: Effect of low flow and high flow oxygen delivery on exercise tolerance and sensation of dyspnea. A study comparing the transtracheal catheter and nasal prongs. *Chest* (1994) 105: 1061-1065.
- Shepard JW Jr and Burger CD: Nasal and oral flow-volume loops in normal subjects and patients with obstructive sleep apnea. *Am Rev Respir Dis.* (1990) 142: 1288-1293.
- Rubin S, Ghuman A, Deakers T, Khemani R, Ross P and Newth CJ: Effort of breathing in children receiving high-flow nasal cannula. *Pediatr Crit Care Med* (2014)15: 1-6.
- Nishimura M: High-flow nasal cannula oxygen therapy in adults. *Journal of Intensive Care* (2015) 3: 15-22.
- Spentzas T, Minarik M, Patters AB, Vinson B and Stidham G: Children with respiratory distress treated with high-flow nasal cannula. *J Intensive Care Med* (2009) 24: 323-328.
- Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH and Iezzoni LI: Consensus-based method for risk adjustment for surgery for congenital heart disease. *J Thorac Cardiovasc Surg* (2002)123: 110-118.
- Muñoz-Bonet JI, Flor-Macián EM, Brines J, Roselló-Millet PM, Cruz Llopis M, López-Prats JL and Castillo S: Predictive factors for the outcome of noninvasive ventilation in pediatric acute respiratory failure. *Pediatr Crit Care Med* (2010) 11: 675-680.
- Pantel H, Hwang J, Brams D, Schnelldorfer T and Nepomnashy D: Effect of Incentive Spirometry on Postoperative Hypoxemia and Pulmonary Complications After Bariatric Surgery: A Randomized Clinical Trial. *JAMA Surg* (2017) 152: 422-428.