High-flow nasal cannula vs standard respiratory care in pediatric procedural sedation: A randomized controlled pilot trial

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Abstract
Introduction: Respiratory instability is frequently observed during pediatric procedural sedation. The aim of this trial was to estimate the impact of high-flow nasal cannula (HFNC) therapy on respiratory stability during sedation for upper gastrointestinal tract endoscopy in children.

Methods: Prospective randomized controlled non-blinded single-center pilot trial. Children were randomly allocated to receive either HFNC (2 L/kg/min) or low-flow nasal oxygen cannula (LFNC, standard care). FiO2 was titrated to maintain SpO2 94% to 98% in both groups. Primary outcome was the number of events of respiratory instability defined by prespecified criteria (hypoxia, hypercapnia, apnea). Secondary outcomes included type and duration of events, number of interventions to regain respiratory stability and cumulative doses of medication.

Results: Fifty children (mean age, 12.3 ± 3.1 years) were enrolled and treated with HFNC (n = 25) or LFNC (n = 25). Patient and intervention characteristics were not different in the two study groups, including total oxygen flow rate. Mean (SD) number of respiratory events in the HFNC group was 2.0 ± 1.9 events compared to 2.0 ± 1.4 events in the LFNC group (P = .65; 95% CI of difference, −1.0 to 1.0). There was no difference for any secondary outcome criteria, percentage of patients for any outcome criteria and no difference in the number of respiratory events or airway management maneuvers per patient between treatment groups.

Conclusions: HFNC did not increase respiratory stability in sedated children undergoing upper gastrointestinal tract endoscopy compared to LFNC.

KEYWORDS
children, endoscopy, high flow therapy, hypoxemia, oxygen therapy
1 | INTRODUCTION

Procedural sedation is frequently performed in children to facilitate painful or unpleasant interventions.1 Procedural sedation may result in adverse respiratory events resulting in hypoxemia, particularly in children, due to a lower oxygen reserve and higher oxygen consumption compared to adults. Rates for respiratory impairments including hypoxemia, hypercapnia, airway obstruction and apnea during pediatric procedural sedation up to 5% have been reported.2 Those respiratory instabilities were also observed in our patients undergoing procedural sedation, for example, upper gastrointestinal tract endoscopy. This emphasizes the need for an adequate respiratory care for children undergoing procedural sedations.

Depending on the depth of sedation, recommended care of patients includes continuous monitoring of vital signs, including heart and respiratory rate, blood pressure, oxygen saturation levels and ventilation as well as the use of supplemental oxygen using a low flow nasal cannula.3,4 Therefore, during procedural sedation a low flow nasal cannula (LFNC) to provide unheated and non-humidified oxygen as required represents the standard respiratory care in our unit.

High-flow nasal cannula (HFNC) is a novel modality of non-invasive respiratory support that provides a heated and humidified continuous gas flow at high flow rates. HFNC generates a continuous positive airway pressure and facilitates CO₂ washout by decreasing dead space5 and has been shown to reduce the rate of hypoxemic events during procedural sedation in adults.6,7 No data exist concerning the use of HFNC in pediatric procedural sedation.

The aim of this study was to assess the efficacy of HFNC to increase the respiratory stability during procedural sedation in children undergoing upper gastrointestinal tract endoscopy compared to standard respiratory care consisting of LFNC. We hypothesized that HFNC would reduce the incidence of events of respiratory instability compared to LFNC.

2 | METHODS

2.1 | Study design and participants

Our hypothesis was tested in a prospective randomized controlled non-blinded parallel group single-center pilot trial. The trial was performed at the procedure room of the pediatric intensive care unit (PICU) at the University Medical Center of Freiburg, Germany from 14th September 2016 to 10th August 2017.

We enrolled children aged 6 to 18 years who were undergoing elective, non-emergency procedural sedation for upper gastrointestinal tract endoscopy. Children with a history of a pneumothorax within 3 months before enrollment, a connective tissue disorder, congenital or acquired upper respiratory tract malformations, missing parental consent or a refused assent of the participant were excluded. All patients were fasting for at least 8 hours before the sedation. Written informed parental consent for the study was obtained for all participants. Children were asked for assent, using a separate age-stratified assent form. The ethics committee of the University of Freiburg, Germany, approved this trial (registration number 143/16), which was conducted according to the Good Clinical Practice Guideline and the Declaration of Helsinki. This trial was prospectively registered at ClinicalTrials.gov, identifier NCT02930525.

2.2 | Randomization and blinding

All patients were randomized to receive either HFNC or LFNC (standard care) as respiratory support during procedural sedation. A permuted block randomization stratified according to age from 6 to 12 years and 13 to 18 years of age with a block size of 6 was performed. The allocation ratio was 1:1, allocation sequence was generated manually, and the allocation concealment was ensured by using identical, opaque, sealed envelopes. An envelope was drawn by the PICU nurse in charge after the patient was transferred to the procedure room. Blinding was not feasible due to the nature of the intervention.

2.3 | Intervention

High flow was provided using a flow generator (Airvo 2, Fisher & Paykel, Auckland, New Zealand) with a continuous flow of heated and humidified ambient air (humidity, 33-45 mg/L at 37 °C) at a rate of 2 L/kg/bodyweight per minute up to a maximum of 30 L/min. In the HFNC group oxygen was applied via the flow generator and was subsequently heated and humidified as mentioned above. An Optiflow nasal cannula (size S, M or L; Fisher & Paykel) served as patient interface in the HFNC group. In the standard care group non-heated humidified low flow oxygen was given via a low flow nasal cannula (Covidien, Neustadt, Germany) from a wall mounted flowmeter.

In both groups (HFNC and standard care) additional oxygen flow was titrated only to maintain a peripheral oxygen saturation of 94% to 98% as measured by pulse oximetry (Masimo, Irvine) after patients were sedated and throughout the endoscopy.

An oxygen supply rate for both groups was calculated by dividing the amount of supplied oxygen per minute (oxygen flow rate) divided by the body weight of the individual participant. This was performed to be able to assess and compare the actual oxygen supply for both groups.

Sedation was performed by a PICU physician using a dose of fentanyl citrate (1.5 µg/kg/dose), followed by repeated doses of 1% propofol (1 mg/kg/dose) until the required level of sedation was achieved as per unit protocol for pediatric procedural sedation. Fentanyl doses were to be repeated for suspected pain or discomfort. Sedation was monitored using the Richmond Agitation Sedation Scale (RASS).

After the desired level of sedation was achieved the patient was positioned for endoscopy which was performed by a pediatric gastroenterologist. Vital signs were constantly monitored (Intellivue, Philips Healthcare, Amsterdam, Netherlands). CO₂ was monitored by...
transcutaneous measurements (TCM CombiM, TCM 4 series, Radiometer Medical ApS, Denmark or SenTec Digital Monitor SDMS-PO2, SenTec AG, Thérywill, Switzerland). Transcutaneous CO2-sensors were calibrated and adjusted to each patient according to an arterialized blood gas analysis that was obtained after induction of sedation. Additional monitoring included pulse oximetry, ECG and respiratory inductance plethysmography.

The patient’s chronic or acute conditions were inquired from the parents or taken from the hospital charts.

2.4 Outcomes

The primary outcome was the number of respiratory events indicating respiratory instability during upper gastrointestinal tract endoscopy. A respiratory event was defined as follows: \( \text{SpO}_2 \leq 93\% \) of \( \geq 15 \) seconds duration or a transcutaneous \( \text{CO}_2 \geq 45 \text{ mm Hg} \) of \( \geq 15 \) seconds duration or apnea as measured by plethysmography of \( \geq 15 \) seconds. Secondary outcomes were: type and duration of events, number of interventions to regain respiratory stability, duration of intervention, cumulative doses of sedatives and postinterventional nausea. All maneuvers additional to oxygen titration to regain respiratory stability like jaw thrust, repositioning of the patient, tactile stimulation, bag-mask-ventilation, or any other intervention were documented. Duration of respiratory events was timed from the onset until the resolution of the event. Duration of the procedure was defined as time from positioning of the patient for the procedure until removal of the endoscope. Duration of sedation was defined as time from first application of intravenous medication until patients regained consciousness with a RASS score of \( \geq -1 \). Post-interventional nausea was defined as self- or caretaker-reported episodes of nausea and vomiting within 24 hours after sedation.

2.5 Statistical analysis

The trial was planned as pilot trial and a number of fifty patients were chosen for feasibility reasons. Qualitative variables were expressed as numbers and percentages. Quantitative variables were expressed as mean (standard deviation) or median (interquartile range) as appropriate. Normality of distribution was tested with the Kolmogorov-Smirnov-Test. We applied nonparametric the Mann-Whitney U test or independent t-test for comparisons of continuous outcomes as appropriate. Categorical outcomes were compared using Fisher’s exact test. Intention-to-treat analysis was applied. Statistical analysis was performed using GraphPad Prism (V. 8, GraphPad Software, San Diego, CA). A two-tailed P-value of <.05 was considered statistically significant.

3 RESULTS

Fifty children were enrolled, were randomized to and received HFNC (n = 25) or LFNC (n = 25). All patients received their intervention as allocated without any premature termination of the intervention. The study flow sheet is given in Figure 1. All patients were spontaneously breathing without respiratory support on ambient room air before the sedation. Indication for the upper respiratory tract endoscopy is given in Table 1.

3.1 Patient characteristics and intervention

Patient characteristics were similar between the two groups except for a higher rate of second or first-hand tobacco smoke exposure (\( P = .02 \)) and a higher prevalence of snoring (\( n = 8 \) vs \( n = 2 \)) in the HFNC-group compared to the LFNC-group (\( P = .04 \)) (Table 1). Choice of sedatives and analgesics was similar between the two groups (\( P = .61 \)). One patient received premedication with midazolam. One patient was sedated using midazolam and ketamine, the remainder received propofol and fentanyl (\( n = 46 \)), or propofol (\( n = 3 \)). No patient received an antiemetic medication prior or after the intervention.

All patients received an upper gastrointestinal tract endoscopy (Table 1). There was no difference in the duration of the upper gastrointestinal tract endoscopy within both groups (8.3 ± 3.8 minutes for HFNC vs 8.2 ± 3.2 minutes for LFNC; \( P = .88 \)) and apart from the gas flow rates according to our protocol there was no difference in any of the procedure characteristics or patient data during the intervention between the two treatment group (Table 2).

3.2 Outcomes

During HFNC 20/25 patients (80%) suffered from any respiratory instability compared to 21/25 patients (84%) receiving standard care (\( P = .10 \)). Apnea was observed in 4/25 cases (16%) during HFNC compared to 6/25 (24%) during standard care (\( P = .72 \)). Hypercapnia occurred in 16/25 patients (64%) during HFNC compared to 17/25 patients (68%) during standard care (\( P = 1.0 \)) and 6/25 patients (24%) treated with each HFNC or standard care received any airway management intervention (\( P = 1.0 \)). There was no difference in the number of respiratory events or airway management maneuvers per patient (Figure 2). There was no difference in the number and duration of respiratory events during upper gastrointestinal tract endoscopy in the HFNC-group compared to the LFNC-group (2.0 ± 1.9 vs 2.0 ± 1.4 events; \( P = .65 \); 95% CI of difference, –1.0 to 1.0; Table 3). There was no evidence of any difference between the two groups secondary outcomes (Table 3). All procedures were performed as planned, no unplanned hospital admission of outpatients or level-of-care increase occurred during this trial.

4 DISCUSSION

In this trial the use of HFNC did not increase respiratory stability compared to low flow oxygen during procedural sedation for upper
gastrointestinal tract endoscopy in children. We had hypothesized that increased nasal flow would improve respiratory stability during procedural sedation by generating a low level continuous positive airway pressure, increased carbon dioxide washout of the pharyngeal dead space and various effects of gas conditioning.

To our knowledge, the use of HFNC during procedural sedation has not been tested in pediatric patients before. Successful oxygenation using HFNC during procedural sedation was reported before in adults undergoing bronchoscopy. In their randomized clinical trial Deitch et al demonstrated that adult patients undergoing procedural sedation experienced less hypoxic episodes if oxygen was applied at 15 L/min compared to room air at the same flowrate. In another trial gas flow rates of 60 L/min compared to 40 L/min were more effective in raising the PaO2/FiO2 ratio at similar FiO2 in adults undergoing bronchoscopy. Similar results by Lin et al found a decreased incidence of hypoxia in a large cohort of adult patients undergoing procedural sedation for gastroscopy when 30 to 60 L/min of oxygen were applied by HFNC compared to 2 L/min of oxygen via LFNC.

However, in these trials, total oxygen exposure of the patients varied significantly between the treatment groups. Large amounts of applied oxygen delivered by HFNC in these trials may rather have been responsible for an improved oxygenation and may have translated into the reduction of hypoxic episodes due to the increased body oxygen stores. The inherent effects of HFNC, however, for example, increased carbon dioxide washout and generation of a mild continuous positive airway pressure on respiratory stability cannot be discriminated in these trials and the effects of potential oxygen toxicity have to be considered.

In our trial we aimed to compare the efficacy of HFNC on respiratory stability at similar rates of oxygen exposure in both groups. Therefore, we only supplied and titrated oxygen to maintain an arterial saturation of ≥94% and not exceeding 98% for both groups. By this approach we achieved comparable oxygen delivery rates to the patients’ nares in both groups independent of total gas flow rates as detailed in Table 2. This allowed us to assess the effects of higher gas flow rates on respiratory stability irrespective of the amount of oxygen delivered. Using this approach, we were not able to observe an increased respiratory stability in patients receiving HFNC. However, estimation of actual alveolar oxygen delivery in non-intubated, spontaneously breathing patients remains difficult; therefore we can only report oxygen delivery to the nares of our patients which may

**FIGURE 1** Study flow sheet
TABLE 1  Patient characteristics

|                          | High flow nasal cannula (n = 25) | Low flow nasal cannula (n = 25) |
|--------------------------|----------------------------------|---------------------------------|
| Age, y                   | 12.2 ± 3.4                       | 12.5 ± 2.8                     |
| Male gender              | 10 (40)                          | 6 (24)                         |
| Body weight, kg          | 45.5 ± 20.7                      | 42.0 ± 15.1                    |
| Body mass index, kg/m²   | 18.9 ± 5.4                       | 17.9 ± 3.2                     |
| ASA risk classification 1 | 5 (20)                           | 4 (16)                         |
| ASA risk classification 2 | 13 (52)                          | 16 (64)                        |
| ASA risk classification 3 | 7 (28)                           | 5 (20)                         |
| Regular smoke exposure (%) | 6 (24)                          | 0 (0)                          |
| Snoring (%)              | 8 (32)                           | 2 (8)                          |
| Diagnostic upper GI tract endoscopy | 22 (88)                   | 23 (92)                        |
| Percutaneous endoscopic gastrostomy | 3 (12) | 2 (8) |

Note: Values are given as mean ± standard deviation or number (%). Abbreviations: ASA, American Society of Anesthesiologists; GI, gastrointestinal tract.
1As assessed at admission to PICU procedure room.
2First- or second-hand smoke exposure.
3Self- or caretaker-reported snoring.

not reflect actual amount of oxygen that was inspired by the patients during both modes of respiratory support. Nevertheless, our data are in line with a recent finding by Riccio et al. who could not observe less arterial oxygen desaturations in obese patients undergoing procedural sedation for colonoscopy when comparing HFNC and LFNC at similar FiO₂. We therefore conclude that the inherent properties of HFNC as discussed above may not increase respiratory stability during short procedural sedations.

We tested our hypothesis in pulmonary healthy children without preexisting pulmonary impairment at the time of the intervention. While some of the underlying principles of HFNC were tested in healthy subjects, most clinical benefit on the use of HFNC was seen in patients suffering from respiratory distress or failure as mentioned above. These subjects may be more prone to alveolar collapse and the increased gas flow of HFNC may support alveolar stability. During procedural sedation in spontaneously breathing children without preexisting pulmonary impairment, alveolar instability and collapse resulting in atelectasis and subsequent hypoxia may not be a predominant pathophysiological feature of respiratory instability. Hypopnea or apnea, as experienced in our patients, may not be alleviated by nasal high flow therapy.

Monitoring carbon dioxide levels is recommended during procedural sedation and may allow for rapid detection of respiratory depression. This can be achieved by using micro stream capnography for end tidal CO₂ measurement. However, in our trial end tidal CO₂ measurement was technically not feasible during HFNC, because the high gas flow rates interfered with exhaled CO₂ sampling. Instead we applied transcutaneous CO₂ monitoring which required some time to achieve a stable CO₂ signal in our study and may therefore not be suitable for routine monitoring of CO₂ during procedural sedation. Furthermore, transcutaneous monitoring of CO₂ partial pressures may require repeated offset calibration. Therefore, the lacking opportunity to perform end tidal CO₂ monitoring appears to be a major disadvantage of HFNC. Concerning ventilation, our results are in line with previous studies where CO₂ levels or the rate of respiratory depression were not improved by HFNC compared to the respective standard of respiratory care.

The effects of HFNC are generated by a certain amount of positive end expiratory pressure, stabilization of the airway, increase in pulmonary functional residual capacity, and reduction of airway dead space by enhancing CO₂ wash out. We assumed that these effects may be beneficial in patients receiving gastrointestinal tract endoscopy since this procedure involves airway manipulation and a considerable time of sedation as opposed to other minor procedures. The use of an endoscopy saving mouthpiece creates an oral leak which might have been detrimental for the efficacy of HFNC in our study. However, generation of a low level CPAP was also noted in patients with an oral leak flow. In conclusion, we cannot speculate on the efficacy of HFNC in other procedures during pediatric procedural sedation where an oral leak flow can be omitted.

TABLE 2  Procedure characteristics

|                          | High flow nasal cannula (n = 25) | Low flow nasal cannula (n = 25) |
|--------------------------|----------------------------------|---------------------------------|
| Duration of sedation, min | 25.4 ± 11.4                      | 35.4 ± 17.6                     |
| Duration of upper GIT endoscopy, min | 8.3 ± 3.8                   | 8.2 ± 3.2                       |
| Dose of fentanyl, µg/kg/h | 2.8 (1.1)                       | 2.4 (1.4)                       |
| Dose of propofol, mg/kg/h | 9.0 (2.9)                       | 9.8 (4.5)                       |
| PICU physician seniority (yrs) | 9.6 ± 6.3                     | 9.4 ± 5.7                       |
| SpO₂ (%)                 | 94.9 ± 15.6                     | 97.9 ± 2.0                      |
| Gas flow rate, L/min     | 29.8 ± 1                        | 2.4 ± 1.8                       |
| Oxygen flow rate, mL/min/kg | 70.7 ± 86.6                   | 73.9 ± 90.5                     |
| pCO₂, mm Hg              | 40.2 ± 4.8                      | 41.2 ± 7.6                      |
| Respiratory rate, min⁻¹  | 19.1 ± 4.0                      | 18.7 ± 4.1                      |
| Heart rate, min⁻¹        | 90 ± 18.1                       | 84.6 ± 15.9                     |
| Mean arterial pressure, mm Hg | 71.7 ± 12.4                   | 67.5 ± 10.9                     |
| RASS-Score               | -3.7 ± 1.4                      | -4.1 ± 1.4                      |

Note: Values are given as mean ± standard deviation. Abbreviations: GIT, gastrointestinal tract; pCO₂, carbon dioxide partial pressure; PICU, pediatric intensive care unit; RASS, Richmond Agitation Sedation Scale; SpO₂, peripheral oxygen saturation.
1During the whole sedation period.
2Years since acquiring medical board licence, number of PICU physicians performing sedation: n = 19.
3Noninvasive oscillometric measurement.
HFNC has been described as an inexpensive intervention.7 However, cost-effectiveness may be highly variable depending on the system used to create HFNC. In our trial costs per patient for heating and humidifying devices and HFNC nasal cannulas were increased by the factor of 60 compared to standard respiratory care.

Side effects of HFNC therapy consisting of nasal or mucosal trauma are common in the neonatal but are less frequently reported in the pediatric or adult population.20,22-25 Abdominal distension and pneumothoraces were described in association with HFNC therapy.20,23-26 Some transient abdominal distension was noted in all our study patients during endoscopy due to either HFNC or iatrogenic gas insufflation via the endoscope but none complained about abdominal discomfort thereafter. A chest x-ray was clinically not indicated in any patient and for ethical reasons we did not perform a routine chest x-ray to rule out a pneumothorax or pneumomediastinum after the intervention. However, we did not find any subcutaneous emphysema, postinterventional nausea was not increased after HFNC and no other side effects such as mucosal dryness, eye irritation, and nasal or eye trauma were observed.

Our study has several limitations. Patients exposed to secondhand smoke and with nocturnal rhonchopathy were more prominent in the HFNC group. For feasibility reasons we did not perform baseline pulmonary function test before inclusion in this study. However, none of the patients had a history consistent with a relevant preexisting respiratory illness or obstructive airway disease at the time of study inclusion. As mentioned above, the presence of an oral leak may have influenced our results, but oral leaks were equally present in both study groups. The use of HFNC in a different patient cohort or for procedures others than endoscopy or in those with pulmonary limitations may reveal different results. We did not use a centralized randomization, using identical, opaque, sealed envelopes in a small sample size with a stratified randomization may still be a potential cause of selection bias. We designed our trial as a pilot study. Therefore, we cannot rule out a beneficial effect of HFNC on respiratory stability during pediatric procedural sedation. We chose a sample size of 50 patients for feasibility reasons; a larger sample size may have uncovered a potential difference in the observed outcomes. Following our experience from this pilot trial we suggest for future testing of HFNC in pediatric procedural sedation to focus on children with an underlying pulmonary impairment and to increase gas

| TABLE 3 Primary and secondary outcome parameter per treatment group |
|---------------------------------------------------------------|
| **High flow nasal cannula (n = 25)** | **Low flow nasal cannula (n = 25)** | **P value** |
| Episodes of respiratory instability (n) | 2.0 ± 1.9 | 2.0 ± 1.4 | .65<br><sup>a</sup> |
| SpO2 ≤ 93% (n) | 0.7 ± 1.0 | 0.6 ± 0.7 | .81<br><sup>a</sup> |
| SpO2 ≤ 89% (n) | 0.5 ± 0.7 | 0.5 ± 0.7 | .80<br><sup>a</sup> |
| Apnea (n) | 0.16 ± 0.4 | 0.24 ± 0.4 | .49<br><sup>a</sup> |
| Hypercapnia (n) | 0.68 ± 0.6 | 0.68 ± 0.5 | .93<br><sup>a</sup> |
| Duration of respiratory instability, min | 3.5 ± 3.4 | 4.7 ± 4.7 | .49<br><sup>a</sup> |
| SpO2 ≤ 93%, min | 0.6 ± 1.1 | 0.8 ± 1.3 | .48<br><sup>a</sup> |
| SpO2 ≤ 89%, min | 0.4 ± 0.6 | 0.5 ± 0.8 | .94<br><sup>a</sup> |
| Apnea, min | 0.1 ± 0.3 | 0.1 ± 0.2 | .53<br><sup>a</sup> |
| Hypercapnia, min | 2.4 ± 2.3 | 3.1 ± 3.4 | .60<br><sup>a</sup> |
| Airway management interventions<sup>b</sup> (n) | 0.4 ± 0.8 | 0.6 ± 1.4 | .91<br><sup>a</sup> |
| Postinterventional nausea | 0 (0) | 3 (12) | .23<br><sup>c</sup> |

Note: Values are given as mean ± standard deviation or number (%), propofol: n = 49, fentanyl: n = 46.

Abbreviations: CO2, carbon dioxide; SpO2, peripheral oxygen saturation.

<sup>a</sup>As defined as any or a combination of the following: bag-mask ventilation, jaw thrust, tactile stimulation, repositioning of the patient.

<sup>b</sup>Mann-Whitney-U-test.

<sup>c</sup>Fisher’s exact test.
flow rates, especially in the presence of a leak flow. The application of gas flow rates exceeding 30 L/min could also have altered our results; however, we were reluctant to increase gas flow rates without further safety data in our patients.

In conclusion, the results of our pilot trial do not suggest an improved respiratory stability using HFNC as respiratory support instead of titrated low flow oxygen in otherwise pulmonary healthy children undergoing procedural sedation for gastrointestinal tract endoscopy.

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