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Original contribution

High-flow versus standard nasal cannula in morbidly obese patients during colonoscopy: A prospective, randomized clinical trial

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ABSTRACT

Study objective: Morbid obesity is associated with adverse airway events including desaturation during deep sedation. Prior works have suggested that proprietary high-flow nasal cannula devices generate positive pressure to all airway structures and may be superior to standard (low-flow) nasal cannula for prevention of desaturation. We hypothesized that, at a similar fraction of inspired oxygen (FiO_2), use of a High-Flow Nasal Cannula (HFNC) at maximum flow rate would result in a lower incidence of intra-procedural desaturation episodes in morbidly obese patients compared to standard nasal cannula (SNC) during deep sedation with propofol.

Design: This is a pragmatic, prospective, randomized clinical trial at one hospital (NCT03148262, UTSW#112016-058). Morbidly obese patients were randomized to HFNC during propofol sedation for colonoscopy. HFNC was performed using maximum flow rates of 60 liters per minute (LPM) and FiO_2 of 0.36–0.40, whereas SNC was performed at 4LPM. The primary endpoint was incidence of arterial oxygen desaturation < 90% measured by pulse oximetry. At midpoint enrollment the Data Monitoring Committee (DMC) performed a pre-planned O'Brien and Fleming futility test.

Main results: Patients were randomized to HFNC (n = 28) or SNC (n = 31). Interim analysis of the primary endpoint showed that the desaturation rates in the HFNC group (39.3%) and the SNC group (45.2%) were not significantly different ($p = 0.79$). The DMC halted the trial at that point due to futility.

Conclusion: **At similar FiO_2**, HFNC was not significantly different from SNC for prevention of arterial oxygen desaturation in morbidly obese patients undergoing propofol sedation for colonoscopy.

1. Introduction

Patients with morbid obesity are often difficult to safely sedate for gastrointestinal endoscopic procedures [1–3]. Morbid obesity is often associated with obstructive apnea, which places the patient at elevated risk for perioperative adverse airway events including hypoxemia [1,3]. Propofol is a common choice for deep sedation during endoscopy, yet propofol may render airway anatomy more prone to obstruction as a consequence of decreased upper airway muscle tone [4]. Cumulatively, these factors can make deep sedation quite challenging in morbidly obese patients.

In the last decade there has been a surge of interest in High-Flow Nasal Cannula (HFNC) oxygen therapy in a variety of patient populations. Originally HFNC was developed for neonates with respiratory distress [5]. Currently this technology has been extended into multiple disparate adult populations [6]. HFNC is delivered by proprietary devices which typically enable control over the percentage of oxygen delivered as well as the flow rate of gas. HFNC systems provide fully humidified gas flows. These systems commonly employ extreme gas flow rates, upward of seventy (70) liters per minute or more [7]. This extreme flow rate provides positive pressure to airway structures, ranging as high as 5–7 cm H_20 [8,9]. It has been hypothesized that HFNC exceeds the inspiratory flow rate, reduces the negative pressure generated by inspiration and impedes expiratory flow, thus reducing the tendency of the airways to collapse [10]. However, the positive pressure generated in the upper and lower airways is variable and dependent on mouth opening and the leak around the cannula. Prior works have demonstrated that although HFNC may not generate pressures used therapeutically in continuous positive airway pressure (CPAP), at an FiO_2 of 21%, the device is sufficient to keep the airways open during sleep and is able to improve OSA in children [11,12]. Other purported advantages of HFNC over traditional nasal cannula delivery systems include maintenance of constant FiO_2, physiologic decrease in anatomical dead space, improved mucocilary clearance, and decreased work

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of breathing [6,13]. HFNC also increases the safe apnea time in patients after induction of general anesthesia via apneic oxygenation [14].

The benefits of apneic oxygenation have been well established in the anesthesia literature. Apneic oxygenation refers to the continuous insufflation of oxygen to an apneic patient with a patent airway to maintain adequate arterial oxygen content in the absence of lung movement [15]. In non-obese patients, successful application of apneic oxygenation during induction of anesthesia has been described using both nasopharyngeal catheters [16–18] and nasal prongs, as well as modified laryngoscopes [19]. Both Baraka et al. and Ramachandran et al. used nasopharyngeal oxygen insufflation in morbidly obese patients during apnea to delay time to desaturation [20,21]. Recently, a more novel method of apneic oxygenation in obese patients using a buccal RAE tube demonstrated a median safe apnea time of 12.5 min [22]. In all studies, a patent airway was maintained throughout the apneic period.

The potential advantages of HFNC over traditional nasal cannula have led to the rapid application of HFNC to anesthetic management [7,23]. However, its role in procedural sedation outside of the operating room has not been fully explored to date. There is insufficient evidence in the literature that suggests HFNC provides benefit over more traditional methods of oxygen delivery during deep sedation in the spontaneously breathing patient. HFNC has been shown to improve patient oxygenation in dental procedures and in bronchoscopy under conscious sedation [24,25]. A small case series has examined HFNC in the setting of propofol sedation for endoscopic procedures in obese patients, and have reported favorable outcomes [26]. Multiple clinical trials listed in the clinicaltrials.gov database are currently evaluating HFNC during procedural sedation (NCT02859597, NCT02930525, NCT03332433, NCT03028688, NCT02968706).

To our knowledge, there are no published prospective, randomized studies that compare the use of the HFNC system to the standard nasal cannula (SNC) in morbidly obese patients presenting for colonoscopy under deep sedation. We performed a randomized, controlled clinical trial to test the hypothesis that, at similar FiO_2, use of the HFNC would result in a lower incidence of desaturation ($SpO_2 < 90\%$) events during procedural sedation compared to the SNC in morbidly obese patients. We chose to expose all patients to a consistent fraction of inspired oxygen (FiO_2 40%) to best isolate the positive pressure effects of the HFNC from the effects pertaining to elevated FiO_2. The primary aim of this study was to determine if the CPAP generated by the HFNC would improve airway obstruction and arterial oxygenation in morbidly obese patients under deep sedation. The primary outcome measure was the incidence of desaturation ($SpO_2 < 90\%$) at any point during the procedure. The secondary outcome measures included an assessment of the need for airway interventions as well as the number of desaturation episodes below 90% per patient in each group.

2. Materials and methods

This study was approved by the University of Texas Southwestern Institutional Review Board (STU 112016-058) and registered with the United States National Clinical Trials Registry (NCT03148262, PI: C. Riccio, Date of registration: 5/8/2017). Written informed patient consent was obtained for all enrolled subjects. This manuscript adheres to the applicable CONSORT guidelines.

This was a prospective, randomized single-center trial at Parkland Hospital in Dallas, Texas. All patients were scheduled for elective colonoscopy under anesthesiologist-directed propofol sedation between May 2017 and August 2017. Eligible patients had a body mass index (BMI) over 40 kg/m^2 and were both male and female between the ages of 18–80 years. Study exclusion criteria included severe chronic obstructive pulmonary disease, pregnancy, propofol allergy, pre-procedure hemodynamic instability and high aspiration risk as determined by the anesthesia team. Subjects who received deep sedation with medications other than lidocaine and propofol were also excluded. Informed consent was obtained by a member of the investigative team in the pre-procedural holding area on the day of the procedure. An obstructive sleep apnea (OSA) screening was performed using the STOP-Bang (SB) questionnaire [27,28]. The SB model has been validated by Chung and Elsaid and shown to have 92.9% to 100% sensitivity in patients with moderate and severe OSA, respectively [29]. More formal testing for OSA was not possible for all patients as it is cost prohibitive and reflects the current availability of polysomnography at Parkland Hospital, a large safety-net hospital system in a major urban center. A diagnosis of OSA from a recent sleep study, however, placed the patient in the high SB group.

Patients were randomized to HFNC versus standard nasal cannula (SNC) intervention, using a randomization scheme created with SAS version 9.3. Two parallel randomization lists were utilized during enrollment, one for patients with $SB < 5$, and the other for patients with $SB \geq 5$. This was done to ensure parity of SB scores between the HFNC and SNC groups. The lists were kept in a locked cabinet in the anesthesia workroom. At the time of enrollment, the study team was unaware of the next intervention and checked the lists only after obtaining informed consent.

All patients were brought into the procedure room and placed on standard monitors, including continuous electrocardiogram, automated blood pressure monitor and pulse oximeter (Masimo SET; Masimo, Irvine, CA, USA). The pulse oximeter was placed on the index finger of the arm opposite to the blood pressure cuff to allow for uninterrupted data and prevention of false drops in saturation upon cuff inflation. The procedure room was equipped with a functional anesthesia machine. All monitors applied to the patient were part of the anesthesia machine monitor and all values were recorded in the associated Electronic Medical Record (EMR). Saturation data in the EMR was populated directly from the pulse oximeter monitor and reflects the average of data points collected every 5 s over a minute duration.

Patients randomized to the HFNC group received the HFNC 5 min prior to the start of sedation at a setting of 36–40% FiO_2. The flow rate was titrated up to the maximum setting of 60 liters per minute (LPM) during this time. In the SNC group, the cannula was placed on the patient 5 min prior to the start of sedation with an oxygen flow rate of 4 LPM, which also provides 36–40% FiO_2 [30,31]. Patients were placed in the lateral position with the head of the gurney elevated approximately 25° to optimize respiratory mechanics and oxygenation in morbidly obese individuals in preparation for sedation [32].

A total of 10 anesthesia providers comprised the investigative team; five physician anesthesiologists and five certified registered nurse anesthetists (CRNAs). At least one member of the study team was present during every procedure to ensure compliance to the protocol and to help monitor depth of sedation and potential airway compromise. All other providers were medically qualified and required to have at least 3 years' experience with airway management. Thus, only senior trainees or fully qualified CRNAs and physician anesthesiologists participated in the study. Both members of the anesthesia care team were present during the procedure, with one designated to care for the patient while the other detailed the procedural events in the EMR. All patients received a protocolized sedation technique, see Appendix 1. After induction of sedation with a lidocaine bolus up to 100 mg and a propofol bolus up to 100 mg intravenously, a propofol infusion was titrated to a Richmond Agitation-Sedation Scale (RASS) score of −3 to −4. The RASS score was designed to have precise, unambiguous definitions for varying depths of sedation based on assessment of arousal, cognition and sustainability. A score of −3 to −4 describes moderate to deep sedation, whereas patients exhibit little or no movement to voice and physical stimulation [33]. All patients remained spontaneously ventilating and expired carbon dioxide (CO_2) tracings in the HFNC group were obtained by placing a simple face mask over the cannula (no additional oxygen was supplied from the mask) with the CO_2 analyzer tubing inserted underneath it, as the extreme flow rates of the HFNC systems can vigorously flush out expired CO_2. $EtCO_2$ tracings in the SNC

group were obtained via the gas sampling line of the SNC (First Breath® Nasal Oxygen Cannula, Smiths Medical; Minneapolis, MN, USA). In all patients, detection of expired CO_2 was achieved, however, quantitative data is unreliable in this setting and was not collected. Anesthesia providers were instructed not to intervene with the patient or propofol infusion unless the patient dropped to an oxygen saturation below 90%. At that point, the provider designated to care for the patient was allowed to intervene by performing any or a combination of: chin lift, jaw thrust, placement of a nasal or oral airway, bag mask ventilation, increasing the FiO_2 and/or decreasing the propofol infusion rate, while the other anesthesia provider made notes in the EMR detailing lowest oxygen saturation observed and type of maneuver performed at that time. Duration of desaturation events was not measured or defined as, oftentimes, a saturation of 90% in sedated morbidly obese patients can result in a potentially greater and more profound degree of hypoxemia. The comfort level of the anesthesia providers with desaturation in this setting was variable as well. Patient and provider safety were of the utmost importance throughout this trial, thus we chose the incidence of desaturation events as the primary endpoint and directed the teams to quickly intervene at an SpO_2 of 90%. At the conclusion of the procedure, patients were allowed to emerge in the procedure room and were then transferred to a Phase 2 recovery unit. The number of desaturations below 90% and all provider interventions noted in the EMR per patient were later entered into a secure study database of prospectively defined variables for analysis.

2.1. Statistical analysis

Data are summarized as mean ± standard deviation (SD) or median (25th and 75th percentile) for continuous data, and as frequency and percentages for categorical data. For continuous data, the characteristics and outcomes for the two intervention groups were compared using Student's *t*-test or Wilcoxon-Mann-Whitney test based on viability of the normality assumption. Viability of the normality assumption was assessed using normal probability plots. Chi-square or Fisher's exact tests were used to compare the two groups with regards to categorical characteristics and outcomes. Level of significance was set at a two-sided p value < 0.05.

The study was powered to detect a 25% difference in desaturation rates between the two study groups with 80% power and a type I error rate of 0.05 and assuming a 50% desaturation rate in the SNC group, following prior publication [3]. The target enrollment was n = 118. Statistical analysis was performed using SAS version 9.3 software.

The Data Monitoring Committee (DMC) was composed of the study's statistician, one of the research assistants and the Principal Investigator. At the interim enrollment point, the DMC reviewed blinded outcome data and performed a futility analysis. O'Brien-Fleming boundary methods for the Lan and Demet's alpha spending function approach were used to derive stopping rules at the interim analysis [34,35]. Based on the results, the DMC decided to end enrollment of the trial and unblind the data.

3. Results

A total of 59 subjects were enrolled and randomized in this trial. Table 1 shows the baseline characteristics of study subjects. Randomization appeared to produce well-balanced groups, although subjects in the SNC group were slightly older and were more likely to have hypertension. No other significant differences were identified between the two groups with regards to demographic and clinical characteristics.

In the SNC group, 14 out of 31 patients (45.2%) had at least one desaturation episode < 90%. In the HFNC group, 11 out of 28 patients (39.3%) had at least one desaturation episode < 90% ($p = 0.79$). (Fig. 1) In total, patients in the SNC group had 44 desaturations episodes compared to 38 desaturation episodes among patients in the HFNC group. The median (25th and 75th percentile) number of intra-

Table 1
Patient demographic and clinical characteristics.

	Standard NC[a] (n = 31)	High Flow NC (n = 28)	*p* value
Demographics			
Age, years, mean (± SD[b])	59 (7)	54 (8)	0.02
BMI[c], mean (± SD), kg/m^2	49 (10)	48 (7)	0.57
Male, n[d] (%)	4 (13)	4 (14)	0.99
African-American/White/ Other n (%)	21 (68)/10 (32)	13 (46)/15 (54)	0.10
Pre-existing conditions n (%)			
Hypertension	28 (90)	18 (64)	0.02
Patients with OSA[e]	5 (16)	5 (18)	0.99
STOPBANG Score, median (IQR[f])	6 (4, 6)	5 (4, 6)	0.70
STOPBANG ≥ 5, n (%)	22 (71)	18 (64)	0.59
Neck Circumference, mean(± SD); cm	43.5 (5.0)	43.3 (5.0)	0.89
ASA[g] score, n (%)			0.61
2	4 (13)	3 (11)	
3	25 (81)	25 (89)	
4	2 (6)	0 (0)	

Values are presented as number and percent (%) for categorical variables and mean (± SD) or median (Inter Quartile Range-IQR) as appropriate for continuous variables.

[a] NC, nasal cannula.
[b] SD, standard deviation.
[c] BMI, Body Mass Index.
[d] n, number.
[e] OSA, Obstructive Sleep Apnea.
[f] IQR, interquartile range.
[g] ASA, American Society of Anesthesiology.

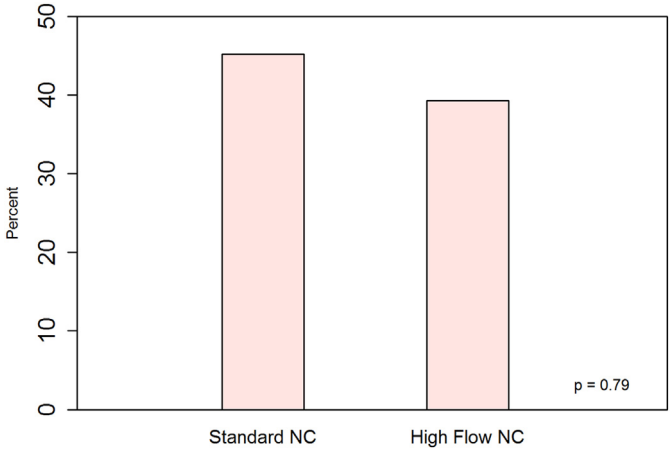

Fig. 1. Proportion of patients with desaturation < 90%.

procedural desaturation episodes also did not differ significantly between the two groups [median (25th and 75th percentile) for HFNC: 0 (0,1), median (25th and 75th percentile) for SNC: 0 (0,2), $p = 0.680$]. Fourteen airway interventions were performed by anesthesia providers in the SNC group and 15 interventions were performed in the HFNC group (all $p > 0.197$). Table 2 shows the primary and secondary endpoint data. Based on an O'Brien-Fleming futility analysis, the DMC ended the trial at the interim point.

In an exploratory secondary analysis, we examined the incidence of desaturation episodes among patients with a higher (≥5) SB score. Analysis of this subgroup was not initially included in the protocol; therefore, the study was not powered to detect a significant difference between these two groups regardless of the stopping point. Statistical calculations were thus not appropriate. Of note, however, within this subgroup, more patients in the SNC group had at least one desaturation episode (7 of 18 (38.9%) in the HFNC vs. 12 of 22 (54.6%) in the SNC). Though only an observation, there appeared to be a trend favoring

Table 2
Desaturation Outcomes, Airway Interventions and Procedural Characteristics.

	Standard NC[a] (n = 31)	High Flow NC (n = 28)	*p* value
Desaturation episode < 90% n[b] (%)	14 (45.2)	11 (39.3)	0.79
Number of desaturation episodes, median (25th, 75th percentile)	0 (0, 1)	0 (0, 2)	0.68
Airway interventions; n (%)			
Chin Lift	10 (32.3)	5 (17.9)	0.24
Jaw Thrust	4 (12.9)	8 (28.6)	0.20
Nasal Airway	2 (6.5)	2 (7.1)	1.00
Minimum recorded SPO_2, mean (± SD)[c]	90.1 (9.8)	90.0 (8.2)	0.84
Desaturation episode < 90% n (%), for patients with STOP-BANG ≥5	12 (54.6%)	7 (38.9)	
Propofol dose; median (25th, 75th percentile); mg			
Induction dose	80 (60, 120)	85 (60, 105)	0.51
Total dose	413 (270, 505)	430 (266, 623)	0.62
Time Intervals; median (25th, 75th percentile); min			
Colonoscopy time	33 (24, 41)	30.5 (21.5, 38.5)	0.73
Anesthesia time	48 (37, 58)	55 (46, 61.5)	0.10
Recovery time	41 (30, 57)	41 (31, 60)	0.50

Values are presented as number and percent (%) for categorical variables and mean (± SD) or median (25th, 75th percentile) as appropriate for continuous variables.
[a] NC, nasal cannula.
[b] n, number
[c] SD, standard deviation

HFNC in the high SB group.

4. Discussion

In this prospective, randomized clinical trial we observed no difference in incidence of desaturations below 90% found in morbidly obese colonoscopy patients treated with supplemental oxygen via SNC (4 LPM) vs. HFNC (FiO_2 0.36–0.4, 60 LPM). There was also no difference found in airway interventions performed by the anesthesia providers between the two groups. Based on these findings the DMC stopped the trial at the interim analysis.

There are several obvious limitations to this study. First, we were not able to confirm the FiO_2 in both groups. Moreover, when using low-flow nasal cannulas, it is generally believed that the delivered FiO_2 varies unpredictably and can be affected by patient-dependent factors, such as tidal volume and respiratory rate. Wettstein et al. measured delivered FiO_2 in healthy volunteers at each liter flow (1–6 L/min) and found that at 4 LPM the FiO_2 varied between 0.40 and 0.50, with higher oxygen concentrations seen in patients breathing with open mouths [31]. A previous study published a calculated FiO_2 of 0.40 at 4 LPM via nasal cannula in normal subjects but did not comment on mouth opening [30]. Our patients were morbidly obese, and demonstrated varying degrees of hypoventilation under deep sedation. We did not note the patients' mouth positions during the procedure. The extent to which this affected the delivered FiO_2 in both groups is unknown. It is possible that the patients in the SNC group received a higher FiO_2 than the HFNC group as pure oxygen filled the nasopharynx prior to inspiration and may explain the lack of difference between the two groups.

We chose 4 LPM as the flow rate for the SNC group for several reasons. First, this is standard practice at our institution and we aimed to design a trial that best reflected current practice in our most challenging patient population so as to generate meaningful results. Additionally, recent work by Pilcher et al. found that high concentration oxygen therapy in morbidly obese patients increased transcutaneous CO_2 when compared with titrated oxygen therapy with a target SpO_2 of 88–92% [36]. Other evidence suggests that administering high levels of oxygen may increase the arterial partial pressure of CO_2 in patients with stable obesity hypoventilation syndrome [37]. Increased atelectasis in obese individuals following induction with high levels of inspired oxygen has also been described [38]. These studies support the notion that oxygen delivered to morbidly obese patients in any clinical setting should be titrated to a lower targeted SpO_2 range to avoid the risks associated with hypercapnia, hypoxia and hyperoxia [39,40]. It is theoretically possible that HFNC at maximum settings may potentially worsen hypercapnia and hypoxemia in morbidly obese patients. Lastly, by using an FiO_2 of 40%, we aimed to expose all patients to a consistent fraction of inspired oxygen between the two devices used in this trial. By equalizing the inspired oxygen content of both devices, we were left with studying the effects of the other purported advantages of the HFNC system independent of the effects of elevated inspired oxygen, mainly, the positive pressure generated by the extreme flow rate.

Another limitation of this trial is that the patients and practitioners were not blinded to the study interventions. The HFNC system is large, bulky and noisy and required set up in the procedure room by the anesthesia technician. The high flow cannulas are considerably larger than the standard cannulas and each connect to different oxygen sources. Different methods of measuring $etCO_2$ were also necessary. Most importantly, the providers needed easy and frequent access to the patients' airways to intervene during desaturation events. Thus, there was no safe and economical way to blind the providers to the study intervention. Of course, knowledge of the intervention may have influenced the anesthesia personnel administering propofol, leading them to adjust the depth of sedation based on their own beliefs of the device being used. To best account for this bias, all providers received a protocol that emphasized an appropriate dosing range for the infusion. Adherence to the protocol was upheld by a member of the investigative team during the procedure. Still, a target-controlled administration of sedation with BIS monitoring may have been more appropriate.

To our knowledge, this is the first trial performed comparing high flow oxygen therapy to standard low flow nasal cannula using similar inspired oxygen levels in morbidly obese patients under deep sedation for colonoscopy. Although prior work in the pediatric population has demonstrated the ability of the HFNC system to overcome upper airway collapse during sleep in OSA children [11,12], we did not find this to be true in our morbidly obese adult patients under deep sedation. Lee et al. reported favorable results in three obese colonoscopy patients, however, the HFNC system was used at maximum flow rate and inspired oxygen levels and no comparisons were made to standard therapy. Also, one patient did experience desaturation events despite using HFNC at maximum settings, requiring airway intervention to improve oxygenation [13].

One of the interesting findings from the secondary exploratory analysis was a trend favoring HFNC in patients with elevated SB scores

≥5. The study was not powered around this sub-group and so no statistical calculations were appropriate. However, a future trial could examine patients with a combination of morbid obesity and elevated SB scores and should include use of the HFNC system at maximum inspired oxygen content (FiO_2 1.0) and flow when comparing to current standard of care therapies. As anesthesiologists increase their presence in areas outside the operating room, more work needs to be done to determine the best method of oxygen delivery during procedural sedation to maximize patient safety, and the role, if any, HFNC plays in this clinical setting.

5. Conclusion

At similar FiO_2, HFNC was not significantly different than SNC for prevention of arterial oxygen desaturation in morbidly obese patients undergoing propofol sedation for colonoscopy.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2018.10.026.

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