Trial Protocol

（Version Number 1.2　　Version Date 2020.03.28）

High-flow Nasal Cannula Oxygenation Reduces the Incidence of Hypoxia During Sedated Gastrointestinal Endoscopy in Patients with Obesity : A Multicentre Prospecticve Randomized Controlled Trial

Sponsor：Renji Hospital, Shanghai Jiaotong University School of Medicine

Department：Department of Anesthesiology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai China

Principal: Diansan Su

Participant: Shanghai Tongji Hospital, Shanghai East Hospital

Statement

As the principal in charge of this clinical trial, I will follow the Ministry of Health's Measures for the Ethical Review of Biomedical Research Involving Humans (2016), the WMA Declaration of Helsinki (2013), the CIOMS International Ethical Guidelines for Human Biomedical Research (2002) and the ethical principles of GCP, and under the guidance of the Good Practice for Drug Clinical Trials. I will use the protocol approved by the Ethics Committee to conduct research according to the requirements of this protocol, so as to ensure the scientific nature of the research and protect the health and rights of subjects. I am aware of the procedures and requirements for proper reporting of serious adverse events, which I will document and report upon request. I certify that the data is accurate, complete, timely, and legally included in the case report form. I will be subject to the supervision or inspection of the inspectors or inspectors dispatched by the sponsor and the inspection and inspection of the drug regulatory department to ensure the quality of clinical trials. I will provide a curriculum vitae to the Ethics Committee prior to the start of the study.

Abstract

Title	High-flow Nasal Cannula Oxygenation Reduces the Incidence of Hypoxia During Sedated Gastrointestinal Endoscopy in Patients with Obesity : A Multicentre Prospecticve Randomised Controlled Trial
Protocol Version	1.2/2020.03.28
Sponsor and Participant	Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai Tongji Hospital, Shanghai East Hospital
Principal	Diansan Su
Quality	Parallel group, pragmatic randomised, superiority trial.
Aim	to investigate whether High-flow nasal cannula (HFNC) oxygenation can reduce the incidence of hypoxia during sedated gastrointestinal endoscopy in patients with obesity.
Sample size	the occurrence of hypoxia during regular nasal cannula oxygenation in obese patients is around 20%. Assuming that HFNC oxygenation can reduce the incidence of hypoxia to 12%, a total Class I error was set α= 0.05, test efficacy power was 0.90, the dropout rate was 10%. Bilateral test, patients are randomly divided into 1:1 groups, and the three components are calculated using PASS software. Therefore, the sample size was estimated to be 972. A total of 1000 patients were enrolled, 500 in the HFNC group and 500 in the regular nasal cannula group, considering the situation may vary.
Subjects	**Inclusion criteria** 1) 18 years old ≤ Age ≤ 70 years old 2) Patients undergo sedated gastrointestinal endoscopy 3) BMI ≥ 28kg/m2 4) Signed the informed consent form 5) American Society of Anesthesiologists (ASA) classification I-II
	Exclusion criteria 1) Coagulation disorders or a tendency of nose bleeding 2) Diagnosed heart disease (heart failure, angina, myocardial infarction, arrhythmia, etc.) 3) Diagnosed lung diseases (asthma, bronchitis,

	COPD, pulmonary bullae, pulmonary embolism, pulmonary edema, lung cancer, etc.) 4) Pregnant women 5) Having liver disease 6) Having kidney disease 7) Increased intracranial pressure 8) Emergency procedure or surgery 9) Having multiple trauma 10) Upper respiratory tract infection 11) Disagree to participate in this experiment 12) Individuals without civil capacity, such as mental disorders 13) Individuals with a history of allergies to drugs used in the research institute.
	Drop off/ Rejection criteria 1) Failure of sedation precludes completion of sedated gastrointestinal endoscopy 2) Had serious adverse events during the trial and had to be discontinued by sedated gastrointestinal endoscopy 3) Not in accordance with the requirements of the protocol
Methods	The enrolled patients were randomly assigned to either of the two groups: regular nasal cannula (control) and HFNC. After obtaining peripheral intravenous access, each patient was asked to lie on their left side; a regular nasal cannula covered by HFNC to blind the patients was then inserted. Patients in both groups received oxygen inhalation at 3 liters/minute through the cannula for approximately 1 minute before they were sedated with 0.5mg/kg propofol. After the patients became sedated, the oxygen flow rate was increased to 6 liters/minute in the regular nasal cannula group, the HFNC was connected to the already set machine (oxygen flow rate of 60 liters/minute, humidification temperature of 37℃, oxygen concentration of 100%) in the HFNC group. Then anesthesiologists administer intravenous propofol 1-2mg/kg and sufentanil 5-7.5ug according to a pre-designed induction protocol. The anesthesiologist closely observed patients once the sedation started and

	continually evaluated the depth of sedation with the Ramsay Sedation Scale (RSS). Once the RSS score was ≥5, the endoscopist inserted the endoscope and started the procedure. Intraoperative sedation maintenance: Ramsay sedation score ≥5, propofol was also intermittently administered at a dose of 0.2-0.5mg/kg until the examination is completed. The patients' heart rate (using continuous ambulatory electrocardiography), blood pressure and SpO2 (using a pulse oximeter) were measured and recorded. Furthermore, the patients' basic information, including name, sex, age, ASA grade, height, weight and BMI, airway examination (Mallampati grade, snoring and polysomnography diagnosis of sleep apnoea syndrome), STOP-Bang questionnaire form and the incidence of perioperative adverse events were recorded. The total dose of propofol was also recorded. When hypoxia occurred, the patient's airway was opened using the jaw-thrust manoeuvre. Mask ventilation and tracheal intubation were performed if severe hypoxia could not be corrected with airway opening. All the adverse events during the procedure were recorded using the reporting tool proposed by the World Society for Intravenous Anaesthesia (SIVA) International Sedation Task Force, which involved the following steps: Step 1: determine whether an adverse event occurred; Step 2: describe the adverse events, including respiratory and sedation-related adverse events; Step 3: record the interventions used to correct the adverse events; and Step 4: record the patient outcome. HFNC oxygenation-related adverse events, including xeromycteria, rhinalgia, pharyngalgia, headache and barotrauma (e.g. pneumothorax and subcutaneous emphysema), were recorded after recovery from anaesthesia.
Statistical Analysis	All tests were two-sided, and $P < 0.05$ was considered to indicate statistical significance, unless otherwise stated. Furthermore, a 95% confidence interval was used. All statistical analyses were conducted using the SAS software version 9.4. Hypoxia events were statistically analysed in both the per-protocol set (PPS)

	and full-analysis set. Continuous variables were expressed as means ± standard deviations or median (25th and 75th percentiles), whereas categorical variables were expressed as number of cases and percentages. For continuous variables, the characteristics and outcomes of the two groups were compared using Student's t-test or Mann–Whitney U test based on the viability of the normality assumption. The viability of the normality assumption was assessed using normal probability plots. Chi-squared or Fisher's exact test was employed to compare the groups in terms of categorical characteristics and outcomes.
Progress Plan	2020.04-2021.03 Formulate the relevant CRF form, pass the ethics, register online and complete 300 cases 2021.03-2022.03 Completed another 700 cases 2022.04-2022.08 Summarize the data, analyze the statistics, and conclude the question
Results	Publish 1-2 SCI article.

Objectives

1.Primary objective

The incidence of hypoxia (75% ≤ SpO2 < 90% for < 60 s).

2.Secondary objectives

2.1. The incidence of subclinical respiratory depression (90% ≤ SpO2 < 95%).

2.2. The incidence of severe hypoxia (SpO2 < 75% or 75% ≤ SpO2 < 90% for ≥60 s).

2.3. The incidence of other adverse events.

2.4. HFNC oxygenation related adverse events.

Background and rationale

Gastrointestinal (GI) endoscopy is the gold standard for diagnosing some GI

diseases, such as GI ulcers, GI tumors, etc. With the development of China's social economy, the demand for GI endoscopy is increasing day by day. There are 75 million endoscopic examinations in the United States every year, of which 68%, about 51 million are GI examinations.[1] Although there are no specific numbers in China, it is estimated that the number of gastroscopes each year is around 13 million. However, during routine GI endoscopy, there are adverse reactions such as nausea, coughing, and pain, which often make most patients refuse to undergo GI endoscopy. In order to increase the comfort of patients during GI endoscopy, the demand and proportion of sedated GI endoscopy have been increasing year by year. During sedated GI endoscopy, patients are quiet, comfortable, with suppressed coughing reflex and significantly reduced pain and stress reactions.[2] At the same time, the advantages bring significant advantages to the operation and detailed examination of gastroscopy physicians. Studies have shown that sedated GI endoscopy can improve the positive diagnosis rate.[3,4] Although the proportion of sedated GI endoscopy in China is far lower than that in developed countries,[5,6] with the development of social economy, the proportion will definitely become closer to that in developed countries.

The combination of propofol and low dose opioids is a commonly used medication regimen in sedated GI endoscopy in most hospitals in China at present. Hypoxemia is the most common complication during sedated GI endoscopy, caused by respiratory depression, airway obstruction, and decreased chest wall compliance,[7] with an incidence rate of approximately 1.8% -69%.[8-13] Insufficient ventilation

caused by various factors is the fundamental cause of hypoxemia, especially in patients with obesity (BMI ≥ 28kg/m^2) where the incidence of hypoxia significantly increases and correction becomes more difficult. The study by Sachin W et al. found that the incidence of hypoxia in patients with obesity undergoing sedated GI endoscopy was significantly higher than that of normal weight.[14] Tiffany S et al. found significant difficulty in mask ventilation in obese patients.[15] At present, China's obesity rate is getting closer to developed countries,[16] and such a high proportion of obese people undoubtedly brings more challenges for sedated GI endoscopy.[17] Long term severe hypoxia can lead to myocardial ischemia, arrhythmia, permanent nerve damage, and even death.[11,18] Reducing hypoxia during sedated GI endoscopy has always been an important clinical issue. Various methods such as endoscopic mask, nasopharyngeal airway, and supraglottic jet ventilation have been used to reduce the incidence of hypoxia, among which nasal cannula oxygen inhalation is the most commonly used option in clinical practice. Bell[19] confirmed that it can reduce the incidence of hypoxia from 77% to 16%.

HFNC oxygenation is a newly developed method of oxygen therapy, which provides a very high flow rate (up to 60L/min) of heated and humidified gas, temperature (31-37 ℃), and oxygen concentration (21-100%) through a special nasal cannula. By providing high flow of oxygen, carbon dioxide in the nasopharynx can be quickly cleared, significantly reducing repeated breathing gases in the dead space of the upper respiratory tract. This generates a continuously variable positive airway

pressure (3-7cmH2O) throughout the entire respiratory cycle, better eliminating carbon dioxide and deepening and slowing breathing, reducing respiratory frequency.[20-24] These mechanisms increase the patient's alveolar ventilation, improve oxygenation, and greatly reduce the occurrence of hypoxia. Lin et al. applied HFNC oxygenation to patients undergoing sedated gastroscopy, they found that HFNC oxygenation can reduce the incidence of hypoxia and severe hypoxia from 8.4% to 0% and 0.6% -0%, respectively.[25] However, the patients included in this study were all ASA I-II grade patients, and their weight was within the normal range. In fact, the proportion of obese patients is high, and this group of patients is the group with the highest incidence of hypoxia. How to reduce the incidence of hypoxia in this group of patients is an urgent clinical problem that needs to be solved. Therefore, this randomized controlled clinical study was designed to verify whether HFNC oxygenation can reduce or even completely avoid the incidence of hypoxia in patients with obesity.

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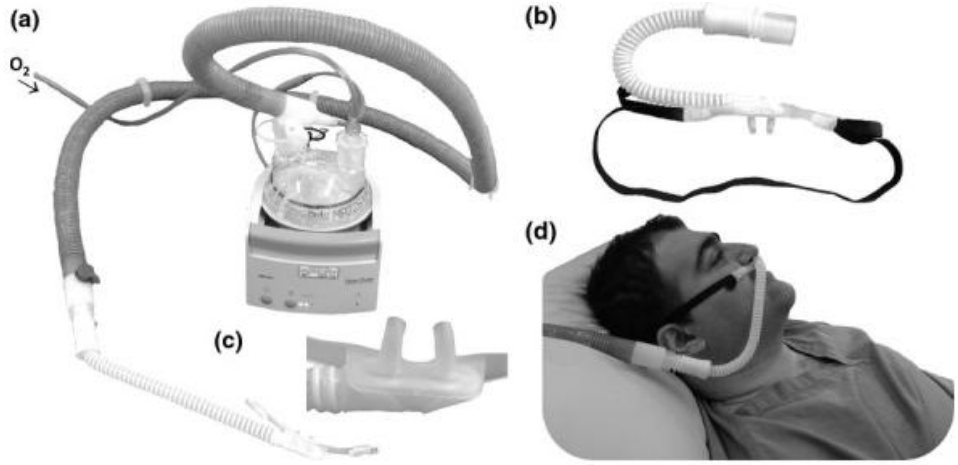


Figure1-2: oxygen humidification device and transnasal oxygen catheter

Participants

This clinical trial has three centers: Renji Hospital Shanghai Jiao Tong University School of Medicine, Shanghai Tongji Hospital, Shanghai East Hospital. This study will enroll 1000 patients with obesity who undergo sedated GI endoscopy (including sedated gastroscopy, sedated colonoscopy and sedated gastroscopy combined with colonoscopy) in the aforementioned hospitals. The ethics committee of Renji Hospital, Shanghai Jiao Tong University School of Medicine approved and supported this clinical trial (KY-2020019).

A summary of the inclusion and exclusion criteria is presented in Table 1.

Table 1 Inclusion/exclusion criteria

Inclusion criteria	**Exclusion criteria**
1) 18 years old ≤ Age ≤ 70 years old	1) Coagulation disorders or a tendency of nose bleeding
2) Scheduled to undergo gastrointestinal endoscopy procedure with sedation	2) Diagnosed heart disease (heart failure, angina, myocardial infarction, arrhythmia,

	etc.)
3) BMI ≥ 28kg/m2	3) Diagnosed lung diseases (asthma, bronchitis, COPD, pulmonary bullae, pulmonary embolism, pulmonary edema, lung cancer, etc.)
4) Signed the informed consent form	4) Pregnant women
5) American Society of Anesthesiologists (ASA) classification I-II	5) Having liver disease
	6) Having kidney disease
	7) Increased intracranial pressure
	8) Emergency procedure or surgery
	9) Having multiple trauma
	10) Upper respiratory tract infection
	11) Disagree to participate in this experiment
	12) Individuals without civil capacity, such as mental disorders
	13) Individuals with a history of allergies to drugs used in the research institute

Outline of Research

1. Participants

Patients with obesity (BMI≥28kg/m2) undergoing sedated GI endoscopy (18 years old ≤ Age ≤ 70 years old).

2. Sample size

According to relevant literature search and preliminary experimental results, the incidence of hypoxia during regular nasal cannula oxygenation in patients with

obesity was approximately 20%. Assuming that HFNC oxygenation can reduce the incidence of hypoxia to 12%, total class I error was set to $\alpha = 0.05$; test efficacy power, 0.90; and dropout rate, 10%. In the bilateral test, the patients were randomly divided into groups in a 1:1 ratio, and the three components were calculated using the PASS software. Therefore, the sample size was estimated to be 972. In total, 1,000 patients were enrolled, 500 in the HFNC group and 500 in the control group, considering the situation may vary.

3.Outline of trial

The enrolled patients will randomly assigned to either of the two groups: regular nasal cannula (control) and HFNC. After obtaining peripheral intravenous access, each patient was asked to lie on their left side; a regular nasal cannula covered by HFNC (AIRVO 2 provided by Fisher & Paykel, Panmure, New Zealand) to blind the patients was then inserted.

In both the groups, the patients' heart rate (using continuous ambulatory electrocardiography), blood pressure and SpO_2 (using a pulse oximeter) will be measured and recorded. Patients in both groups receive oxygen inhalation at 3 liters/minute through the cannula for approximately 1 minute before they were sedated with 0.5mg/kg propofol. After the patients become sedated, the oxygen flow rate is increased to 6 liters/minute in the regular nasal cannula group, the HFNC is connected to the already set machine (oxygen flow rate of 60 liters/minute, humidification temperature of 37℃, oxygen concentration of 100%) in the HFNC

group. Then anesthesiologists administer intravenous propofol 1-2mg/kg and sufentanil 5-7.5ug according to a pre-designed induction protocol. The anesthesiologist closely observes patients once the sedation started and continually evaluates the depth of sedation with the Ramsay Sedation Scale (RSS). Once the RSS score is ≥5, the endoscopist will insert the gastroscope and start the procedure. Intraoperative sedation maintenance: Ramsay sedation score ≥5, propofol is also administered intermittently with a dose of 0.2-0.5mg/kg until the examination is completed.

The basic information of the participants and the incidence of perioperative related adverse events will be recorded, including: name, gender, age, ASA grade, height, weight, BMI, airway examination (Mallampati grade, snoring, and polysomnography diagnosis of sleep apnea syndrome), STOP-Bang questionnaire form. The total dose of propofol will be recorded. When hypoxia occurs, they will be improved by opening the airway using the jaw-thrust maneuver. Mask ventilation and tracheal intubation are necessary if severe hypoxia can not be corrected by opening the airway. All adverse events that occur during the procedure will be recorded using the reporting tool proposed by the World Society for Intravenous Anaesthesia (SIVA) International Sedation Task Force, which involves the following steps: Step 1: determine whether an adverse event occurs; Step 2: describe the adverse events, including respiratory and sedation-related adverse events; Step 3: record the interventions used to correct the adverse events; and Step 4: record the patient

outcome. HFNC oxygenation related adverse events, including xeromycteria, rhinalgia, pharyngalgia, headache, and barotrauma (eg, pneumothorax and subcutaneous emphysema), will be recorded after recovery from anesthesia.

Basic Information of Subjects and Procedure

Filter number:
Central random number:

Name		**Gneder**		**Age**		**ASA Classification**	
Procedure Type	☐ **Gastroscope** ☐ **Colonoscopy** ☐ **Gastrointestinal endoscopy**						
Height	cm	**Weight**	Kg	**BMI (Kg/m^2)**			
Procedure Time(min)	min						
Total Dosage of Sufentanil (ug)	ug						
Total dosage of propofol (mg/kg)	mg/Kg（ mg）						
Airway examination	**Mallampati Class**	☐ I ☐ II ☐ III ☐ IV					
	Snore	☐Yes ☐ No					
	OSAHS	☐ Yes ☐Uncertain* ☐ No					

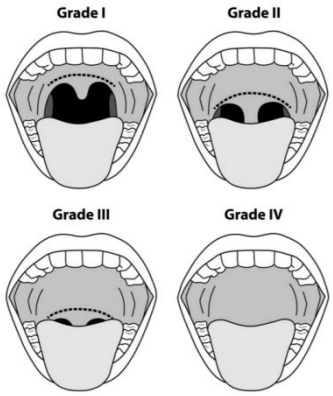
* If the patient is uncertain of whether they have OSAAHS, STOP Bang questionnaire needs to be completed to assess the risks of OSAHS. (low risk group: total score < 3 , high risk group: total score ≥ 3)

STOP Bang Questionnaire

Variables	**Scores (No=0 point, Yes=1 point)**
Snoring	☐ No ☐ Yes

Tiredness	☐ No ☐ Yes
Observed Apnea	☐ No ☐ Yes
High Blood Pressure	☐ No ☐ Yes
BMI>35kg/m2	☐ No ☐ Yes
Age>50 years old	☐ No ☐ Yes
Neck circumference>40cm	☐ No ☐ Yes
Gender = Male	☐ No ☐ Yes
Total points	
Risk grouping	☐ Low risk group total: score < 3 ☐ High risk group total: score ≥ 3

Mallampati Class



Grade I: The soft palate, pharyngeal isthmus arch, uvula, and basal column can be seen; Grade II: The soft palate, pharyngeal isthmus arch, and part of the uvula are visible; Grade III: Only the soft palate is seen; Grade IV: The soft palate is not visible.

Multisociety sedation curriculum for gastrointestinal endoscopy" Gastrointest Endosc 2012;76:el-25

SPO2 Changes during Intravenous Anesthesia

HFNC group	Pre-intravenous anesthesia SpO2 (%)	SpO2 %
	Minimum SpO2 (%) during intravenous anesthesia	SpO2 %
	Duration of hypoxia (seconds)	
	During intravenous anesthesia SpO2 < 90% (Positive event)	☐ Yes ☐ No
Regular nasal cannula group	Pre-intravenous anesthesia SpO2 (%)	SpO2 %
	Minimum SpO2 (%) during intravenous anesthesia	SpO2 %
	Duration of hypoxia (seconds)	
	During intravenous anesthesia SpO2 < 90% (Positive event)	☐ Yes ☐ No

Classification of Hypoxia

Subclinical Respiratory Depression（90%≤SpO2≤95%）	☐
Hypoxia（75%≤SpO2≤89%，for＜60 s）	☐
Severe Hypoxia（SpO2＜75%，或 SpO2＜90%，for＞60 s）	☐

If the SPO2 is less than 90% during intravenous anesthesia, the airway is opened sequentially until the patient's SPO2 is greater than 90%.

The last way to open the airway with SPO2 greater than 90%:

☐1.a chin lift or jaw thrust maneuver

☐2.artificial mask ventilation

☐3.tracheal intubation

Ramsay Sedation Scale (RSS)

Score	Level of Sedation
1	Patient is anxious and agitated or restless, or both
2	Patient is co-operative, oriented, and tranquil
3	Patient responds to commands only
4	Patient exhibits brisk response to light tactile stimuli or loud auditory stimulus
5	Patient exhibits sluggish response to light tactile stimuli or loud auditory stimulus
6	Patient exhibits no response

Adverse events of anesthesia and sedation

Step 1: Was there one or more adverse events associated with this sedation encounter?

☐No, this form is now complete.	☐ Yes, fill out remainder of form below.

Step 2: Please DESCRIBE the adverse event(s). Check all that apply.

Minimal risk descriptors	**Minor risk descriptors**	**Sentinel risk descriptors**	
☐ Vomiting/Retching	☐ Oxygen desaturation (75-90%) for < 60s	☐ Oxygren desaturation, severe (<75% at any time) or prolonged(<90%	Other, specify below

			for >60s)	
☐ Sub-clinical respiratory depression	☐ Apnoea not prolonged		☐Apnoea, prolonged (>60s)	
☐Muscle rigidity, Myoclonus	☐ Airway obstruction		☐Cardiovascular collapse/shock	
☐ Hypersalivation	☐ Failed sedation		☐Cardiac arrest/absent pulse	
☐ Paradoxical response	☐Allergic reaction without anaphylaxis			
☐ Recovery agitationc	☐ Bradycardiatf			
☐ Prolonged recovery	☐ Tachycardiaf			
	☐ Hypotensionf			
	☐ Hypertensionf			
	☐ Seizure			
Step 3: Please note the INTERVENTIONS performed to treat the adverse events(s). Check all that apply.				
Minimal risk	**Minor risk**	**Moderate risk**	**Sentinel intervention**	
☐No intervention performed	☐Airway repositioning	☐Bag valve mask-assisted ventilation	☐ Chest compressions	Other, specify below
☐ Tactile stimulation	☐Tactile stimulation	☐ Laryngeal mask airway	☐Tracheal intubation	
☐ Additional sedative(s)	or the administration of:	☐ Ora/nasal airway	or the administration of:	
☐ Antiemetic	☐Supplemental oxygen, new or increased	☐ CPAP	☐Neuromuscular block	
☐ Antihistamine	☐Antisialogogue	or the administration of:	☐Pressor/epinephrine	

<table>
<tr><td rowspan="3"></td><td rowspan="3"></td><td>☐ Reversal agents</td><td rowspan="3">☐Atropine to treat bradycardia</td><td rowspan="3"></td></tr>
<tr><td>☐ Rapid i.v.fluids</td></tr>
<tr><td>☐Anticonvulsanti.v.</td></tr>
<tr><td colspan="5">Step 4: Please note the OUTCOME of the adverse events(s). Check all that apply.</td></tr>
<tr><td>Minimal risk outcome</td><td colspan="2">Moderate risk outcome</td><td colspan="2">Sentinel outcome</td></tr>
<tr><td rowspan="3">☐No adverse outcome</td><td colspan="2" rowspan="3">☐Unplanned hospitalisation or escalation of care</td><td>☐ Death</td><td rowspan="3">Other, specify below</td></tr>
<tr><td>☐Permanent neurological deficit</td></tr>
<tr><td>☐Pulmonary aspiration syndromei</td></tr>
<tr><td colspan="5">Step 5: Assign a SEVERITY rating to the adverse event(s) associated with this sedation encounter.</td></tr>
<tr><td colspan="5">If there are any options checked in the Sentinel columns above, then this is a Sentinel adverse event.</td></tr>
<tr><td colspan="5">If the most serious option(s) checked above are Moderate risk, then this is a Moderate risk adverse event.</td></tr>
<tr><td colspan="5">If the most serious option(s) checked above are Minor risk, then this is a Minor risk adverse event.</td></tr>
<tr><td colspan="5">If the most serious option(s) checked above are Minimal risk, then this is a Minimal risk adverse event.</td></tr>
</table>

Footnotes:

a. “Sub-clinical respiratory depression” is defined as capnographic abnormalities suggesting respiratory depression that do not manifest clinically.

b. “Paradoxical response” is defined as unanticipated restlessness or agitation in response to sedatives.

c. “Recovery agitation” is defined as abnormal patient affect or behaviors during the recovery phase that can include crying, agitation, delirium, dysphoria, hallucinations, or nightmares.

d. “Prolonged recovery” is defined as failure to return to baseline clinical status within 2 hours.

e. “Failed sedation” is defined as inability to attain suitable conditions to humanely perform the procedure.

f. Alteration in vitals signs (bradycardia, tachycardia, hypotension, hypertension) is defined as a change of >25% from baseline.

g. “Cardiovascular collapse/shock” is defined as clinical evidence of inadequate perfusion.

h. Examples of “escalation of care” include transfer from ward to intensive care, and prolonged hospitalisation.

i. “Pulmonary aspiration syndrome” is defined as known or suspected inhalation of foreign

material such as gastric contents into the respiratory tract associated with new or worsening respiratory signs.

j. "Sentinel" adverse events are those critical enough to represent real or serious imminent risk of serious and major patient injury. Once recognized, they warrant immediate and aggressive rescue interventions. Once clinically concluded, they warrant immediate reporting within sedation care systems, and the highest level of peer scrutiny for continuous quality improvement.

k. "Moderate" adverse events are those that, while not sentinel, are serious enough to quickly endanger the patient if not promptly managed. Once clinically concluded, they warrant timely reporting within sedation care systems, and periodic peer scrutiny for continuous quality improvemet.

l. "Minor" adverse events are those encountered periodically in most sedation settings, and that pose little threat given appropriate sedationist skills and monitoring.

m. "Minimal" adverse events are those that alone present no danger of permanent harm to the patient.

Clinical Trial Serious Adverse Event Reporting Form（SAE）

<table>
<tr><td colspan="2">Report Type</td><td colspan="2">□First report
□Follow-up report
□Summary report</td><td>Report Time</td><td>Y M D</td></tr>
<tr><td colspan="2">Hospital</td><td colspan="2"></td><td>Department</td><td></td></tr>
<tr><td colspan="2">Principal</td><td colspan="2"></td><td>TEL</td><td></td></tr>
<tr><td colspan="2">Clinical Trial Name</td><td colspan="4"></td></tr>
<tr><td rowspan="2">Charact-eristics of subjects</td><td>Name Abbreviation:</td><td>Date of birth:</td><td>Gender:
□M □F</td><td>Height(cm):</td><td>Weight(Kg):</td></tr>
<tr><td colspan="5">Comorbidities and treatments：□Yes □No
1.Disease： Drug： Dosage：
2.Disease： Drug： Dosage：</td></tr>
<tr><td colspan="2">Medical Terminology (Diagnostic) for SAE</td><td colspan="4"></td></tr>
<tr><td colspan="2">SAE's Situation</td><td colspan="4">□Death _ _ _ _ _ Y_ _ _M_ _ _D;
□Resulting in hospitalization;</td></tr>
</table>

	□Prolonging hospital stays; □Permanent disability; □dysfunction; □Causes congenital malformations; □Life-threatening; □Other:
Time of SAE: **_ _ _ Y_ _ _M_ _ _D**	**Informed Investigator's Time of SAE：** **_ _ _ Y_ _ _M_ _ _D**

Measures taken on the subject	□Keep research □suspension research □End research □Paused and then resumed
SAE's Final Result	□ Symptoms cure（ Sequelae □Yes □No） □ Symptoms persist □ Other
Relationship of SAE to the trial	□ Definitely related □ Probably related □ Probably unrelated □ Definitely not □ Uncertain
SAE's Report	Domestic: □Have □No □Uncertain; Abroad: □Have □No □Uncertain
Details of the occurrence and treatment of SAEs	
Follow-up	

Hospital:	**Position of the Reporter/Title：**	**Reporter (Investigator) signature:**

Record of Adverse Events Related to HFNC Oxygenation Therapy Device (Airvo2) After Awakening

Dry/Xeromycteria	□No □Yes
Headache	□No □Yes
Nasal mucosal injury and bleeding (blood loss and duration)	□No □Yes blood loss (）ml duration ( ) min
Barotrauma (pneumothorax,subcutaneous emphysema, lung injury)	□No □Yes Specific types of barotrauma：

Methods

1.Enrollment

1.1 Inclusion criteria

1) 18 years old ≤ Age ≤ 70 years old
2) Scheduled to undergo gastrointestinal endoscopy procedure with sedation
3) BMI ≥ 28kg/m2
4) Signed the informed consent form
5) ASA classification I-II

1.2 Exclusion criteria

1) Coagulation disorders or a tendency of nose bleeding

2) Diagnosed heart disease (heart failure, angina, myocardial infarction, arrhythmia, etc.

3) Diagnosed lung diseases (asthma, bronchitis, COPD, pulmonary bullae, pulmonary embolism, pulmonary edema, lung cancer, etc.)

4) Pregnant women

5) Having liver disease

6) Having kidney disease

7) Increased intracranial pressure

8) Emergency procedure or surgery

9) Having multiple trauma

10) Upper respiratory tract infection

11) Disagree to participate in this experiment

12) Individuals without civil capacity, such as mental disorders

13) Individuals with a history of allergies to drugs used in the research institute

1.3.Drop off/ Rejection criteria

1) Failure of sedation precludes completion of sedated gastrointestinal endoscopy

2) Had serious adverse events during the trial and had to be discontinued by sedated gastrointestinal endoscopy

3) Not in accordance with the requirements of the protocol

2.Allocation

1) Control group: regular nasal cannula group

2) Experimental group：HFNC group

3.Randomization

A biostatistician, who will not take part in the data management and statistical analyses, generates the randomization sequence. The PROC PLAN program in SAS (version9.0) was used to generate the sample randomization sequence using 1:1 allocation with block Z 340 and length Z 6 and stratified by the coordinating center. The results of the randomization will be sealed in sequentially numbered envelopes. Consecutively recruited patients are assigned to the regular nasal cannula or HFNC group on opening the envelopes.

4.Blinding/Unblinding

1) blinding

After the interventions are assigned, only the trial participants will be blinded. Patients will be masked because they all undergo the procedure in the same room in each center, and the HFNC oxygenation device is always at their bedside. Each patient will be inserted a regular nasal cannula covered by HFNC. Patients in both groups receive oxygen inhalation at 3 liters/minute through the cannula for approximately 1 minute before they are sedated with 0.5mg/kg propofol. After the patients become sedated, the oxygen flow rate will increase to 6 liters/minute in the regular nasal cannula group, the HFNC will be connected to the already set machine

(oxygen flow rate of 60 liters/minute, humidification temperature of 37℃, oxygen concentration of 100%) in the HFNC group. The researcher will ensure that participants are not aware of their own or other's assignment.

2）unblinding

As the trial is single-blind, patients interested in knowing their group could be informed by the investigator following the analysis of results.

5.remediation and supportive care

When there is an emergency or accident during the operation, the patient is mainly treated, the patient's safety is put first, and the patient is rescued and treated according to the clinical routine.

Test Program

1. Subject managements

1) Recruitment

This study will include the patients with obesity who are scheduled to undergo GI endoscopy with sedation. The patients (BMI ≥ 28kg/m2) who met the inclusion criteria will be preliminarily screened by the investigators and recruited by distributing recruitment materials to patients and their families. Additionally, we will put up recruitment posters in the endoscopy centers explaining the advantages of our trial. The HFNC that will be used in our trial are free, and the trial is beneficial for participants.

The entire process of recruiting participants and obtaining their consent by the

members of the research team will be consistent with GCP.

2) Informed Consent

Trained anesthesiologists will explain this trial to the potential participants in detail, and the informed consent form will be provided. Participants can decide whether they wish to participate in the trial after sufficient time to deliberate. Subsequently, the participant or his/her trustee or guardian can sign the informed consent form, and they can withdraw at any time during the trial. Following this, baseline data will be collected from the patients, and they will be randomly allocated. Participants can contact our team if they have any health concerns during the trial. The entire process of recruiting participants and obtaining their consent by the members of the research team will be performed in accordance with good clinical practice (GCP). In case of any AEs during the trial related to the study procedure or not, the researchers will immediately report to the director in charge of the clinical trial of the research institution and contact Professor Diansan Su.

3) Check Inclusion / Exclusion Criteria

Subjects are selected strictly accordance to the inclusion and exclusion criteria, and they need to be checked before admission to the operating room and before anesthesia induction.

4) Filter the assignment of the number

Each subject who signs the informed consent form is assigned a screening number, which is assigned according to the time of signing.

5)Assignment of random group numbers

Enrollment is contested among different sites, and a central randomized system will be designed by statistical professionals according to the clinical study protocol. Participants will be allocated by a central randomized system after entering the outpatient GI endoscopy operating room and before anesthesia induction. After allocation, HFNC oxygenation will be performed or not by group. During the whole process of the clinical trial, the information of the random number and the randomization table will be kept confidential to the participants.

Duration of Surgery

The duration of surgery is defined as the time from the beginning to the end of the gastrointestinal endoscopy, excluding the time of resuscitation.

Clinical Criteria for Early Termination of the Trial

Participants with serious adverse events and/or changes in anesthesia mode during the course of the trial.

Data Management

The case report form (CRF) of the respective patients will be entered and/or filled in for all the collected patient data during this clinical trial. The study number, subject number, date of subject information, and informed consent will be appropriately documented in the patient CRF. We will archive the source data as per GCP guidelines. The data manager will be responsible for data processing and will conduct regular monitoring according to the sponsor’s standard operating procedures

to ensure that the dates are adequate, accurate, and complete. The source data lock will occur only after the completion of the the quality assurance procedures.

Confidentiality

Participant information will be confidential and managed according to the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee approval. The confidentiality of the data collected during the course of the research will be strictly maintained, and only the members of the trial team (or individuals from the sponsor organization or center sites relevant to the trial) will be allowed to access the data. All documents containing patient information are stored in a specific cabinet in the anesthesia department, locked and keyed for safekeeping. The permission of the principal investigator is required for removal or access of the data. The participants will be allocated an individual trial identification number and their details will be stored in a secure database. This database is maintained by professional researchers, and only the principal investigator has access to the data set. The anonymized trial data are not to be shared with other researchers.

Frequency and Plans for Auditing Trial Conduct

The investigators shall maintain all study data according to GCP requirements. The original study data and information will be retained for at least 5 years following trial completion. Data security and monitoring reports will be submitted to the ethical committee every 3 months.

Adverse Event Reporting and Harms

The nasal catheter that HFNC used is similar to the regular nasal cannula and does not have any additional risks. To date, to the best of our knowledge, there has been no evidence that this study may cause any risk or discomfort to the participants.

We will record any AEs that occur during the clinical trial, regardless of whether these events were associated with the intervention. Additionally, all the expected and unexpected trial-related AEs will be reported in the trial publications.

Ethics Approval and Consent to Participate

The Ethics Commission of Renji Hospital Shanghai Jiaotong University School of Medicine approved and supported this clinical trial (KY2021-014).

Statistical Methods

1.Statistical methods for primary and secondary outcomes

1.1 Data selection for statistical analysis

1) Full analysis set (FAS): According to the principle of intention-to-treat analysis, the full analysis set will include all subjects who are randomized to the study and receive the study treatment.

2) Per-protocol set (PPS): The PPS population will include all FAS patients without major protocol deviations that influence the evaluation of primary outcome, such as the different dosage of sufentanil during induction or lack of primary outcome data. The efficacy analysis will be performed on the FAS and PPS.

3) Safety analysis set (SAS): The safety population will comprise all subjects who

receive the study treatment. Analyses of safety data in the study will be based on the safety population.

1.2 Statistical analysis plan

All tests will be two-sided, $P<0.05$ will be considered statistically significant, unless otherwise stated, and a 95% confidence interval will be used for the confidence interval. SAS 9.4 software will be used to conduct the statistical analysis. A statistical analysis of hypoxia events will be performed in both the per-protocol set (PPS) and the full analysis set (FAS).Data will be summarized as mean ± standard deviation (SD) or median (25th and 75th percentile) for continuous data, and as numbers of cases and percentages for categorical data. For continuous data, the characteristics and outcomes for the two intervention groups will be compared using Student's t-test or Wilcoxon-Mann-Whitney test based on viability of the normality assumption. Viability of the normality assumption will be assessed using normal probability plots. Chi-square or Fisher's exact tests will be used to compare the two groups with regards to Categorical characteristics and outcomes.

1.3 Additional analyses

Safety analysis: general safety evaluations will be based on the incidence and type of AEs. Safety variables will be tabulated and presented for all the patients in safety sets. AEs will be coded using the tools proposed by the World Society of Intravenous Anesthesia International Sedation Task Force. The number (%) of subjects with any AEs will be summarized and compared via $\chi 2$ test, continuity

correction $\chi 2$ test, or Fisher's exact test.

2. Methods for additional analyzes

The association between the baseline characteristics and intervention and the risk of total hypoxia cumulative incidence will be examined using univariable- and multivariable-adjusted logistic regression models. The results will be presented as the relative risk and corresponding 95% confidence intervals.

3.Methods in the analysis to handle protocol nonadherence and any statistical methods to handle missing data

Statistical analysis will be performed based on intention-to-treat. Regardless of protocol adherence, the results of the outcome analyses will be randomly analyzed. The frequency and type of missingness of all the variables will be screened. If missingness is >5% of any variable, we will use multiple imputations. Complete case analysis will be performed as a sensitivity analysis, in case of missing data and imputation.