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Sufentanil target controlled infusion (TCI) vs remifentanil TCI for monitored anaesthesia care for patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy: protocol for a prospective, randomized, controlled study

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Keywords: Adult anaesthesia; Endoscopic surgery; Anaesthetics

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ABSTRACT

Introduction

The use of monitored anaesthesia care (MAC) is necessary and ubiquitous for fiberoptic bronchoscopy. The efficacy and safety of the MAC with sufentanil target controlled infusion (TCI) and remifentanil TCI in patients with severe tracheal stenosis are still unknown.

Methods analysis

This study is a prospective, investigator-initiated, two-arm, randomized control trial to compare the efficacy and safety of sufentanil TCI with remifentanil TCI in patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy. 270 patients will be randomly assigned to the sufentanil TCI group or remifentanil TCI group, with a 1:1 ratio in two groups. The primary outcome is the incidence of hypoxemia (an oxygen saturation of <90%).

Ethics and dissemination

The study has been approved by the Medical Ethics Committee of Shanghai Pulmonary Hospital. The results will be submitted for publication in peer-reviewed journals.

Trial registration number ChiCTR2100043380

Strengths and limitations of this study

- This study is an investigator-initiated, randomized, controlled trial, comparing two MAC strategies.
- This study includes only subjects with severe tracheal stenosis.
- The main limitation of our study is that considering the characteristics of the two MAC strategies, the overall trial is not double-blind.

INTRODUCTION

Since the introduction of the flexible fiberoptic bronchoscope, bronchoscopy has been widely used as a diagnostic tool in the field of clinical respiratory medicine. Approximately 500,000 fiberoptic bronchoscopy are performed in the United States

annually[1]. Sedation is now generally recommended for all patients undergoing fiberoptic bronchoscopy unless a specific contraindication to sedation exists[2-4]. Sedation during fiberoptic bronchoscopy improves patient comfort and tolerance, and enhances the willingness to repeat the procedure, without increasing complications[3 5 6].

Bronchoscopy has been an integral part of the diagnosis and treatment of patients with severe tracheal stenosis[7]. Patients affected by severe tracheal stenosis develop symptoms such as stridor, dyspnea, voice changes, mucus production increasing, and persistent cough[8]. Most patients require sedation and analgesia to tolerate fiberoptic bronchoscopy. Anaesthetic management for patients with severe tracheal stenosis during fiberoptic bronchoscopy procedures has always been challenging, and there is no standardized practice currently[3 9].

Remifentanil has a rapid onset of action and elimination half-life and a predictable duration of action with no accumulation of effect on repeated dosing or with continuous infusion, which making it suitable for anaesthesia management of diagnostic and therapeutic bronchoscopy[10-15]. The degree of the noxious stimulation caused by the insertion and manipulation of a bronchoscope is often similar to a surgical incision. Remifentanil might cause respiratory depression or hemodynamic instability when effectively inhibiting operational stress, which is often very dangerous for patients with severe tracheal stenosis[14 16 17]. Sufentanil is a more potent opioid than remifentanil, its analgesic effect lasts longer and it is superior in terms of hemodynamic stability. Sufentanil has a longer half-time as compared with remifentanil, but TCI will prevent long-acting opioid-induced accumulation and allow rapid recovery from anaesthesia[18]. There have been no detailed investigations on the efficacy and safety of monitored anesthesia care (MAC) using sufentanil or remifentanil TCI in patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy. The aim of our study is to compare sufentanil TCI with remifentanil TCI in patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy.

Objectives

We aim to conduct a prospective randomized controlled trial comparing sufentanil TCI with remifentanil TCI and assume that sufentanil TCI would decrease the incidence of hypoxemia.

Primary objective

Determine the incidence of hypoxemia of MAC with sufentanil TCI versus MAC with remifentanil TCI in patients with severe tracheal stenosis undergoing bronchoscopy.

METHODS AND ANALYSIS

Study design

This is a single-center, randomized, investigator-initiated clinical trial of 270 patients with severe tracheal stenosis that requires fiberoptic bronchoscopy. The CONSORT flow chart is presented in Figure 1. A SPIRIT figure is included in Figure 2 with a checklist included as an additional document (Supplementary file 1). Patients will be randomly assigned to one of two groups. Group S will be received sufentanil TCI and Group R will be received remifentanil TCI.

Inclusion criteria

All patients treated with fiberoptic bronchoscopy in Shanghai Pulmonary Hospital will be screened for eligibility in strict accordance with the inclusion and exclusion criteria. Tracheal stenosis is defined as narrowing of the endotracheal lumen. The diagnosis will be determined by the same respiratory physician together with the same endoscopist. The inclusion criteria are patients aged 18–65 years, with the American Society of Anesthesiologists (ASA) physical status classifications I–III and Cotton-Myer grades II-III (the narrow of the endotracheal lumen is more than 50%). The exclusion criteria are shown in Table 1.

Table1. Summary of exclusion criteria of the trial.

Exclusion criteria
BMI>30 or < 18.5
Baseline oxygen desaturation (resting SpO_2 <90%)
Chronic opioid treatment, substance abuse or drug use

Pregnancy
History of allergy to related drugs
Severe coagulation dysfunction
Severe hepatic and renal dysfunction
Gastroesophageal reflux disease
History of abnormal recovery from anaesthesia
No informed consent

Recruitment

Consecutive patients who present to respiratory clinics at Shanghai Pulmonary Hospital with a diagnosis of tracheal stenosis and meet the inclusion criteria will be offered the opportunity to enroll in our study. We will inform them of details about our study. All patients will be provided with full information of their part in our study and assure that their information will be kept strictly confidential.

Information consent

Informed consent will be obtained from each patient or legally authorized representative (LAR) prior to enrollment in our study. This will provide a clear understanding that their participation is entirely voluntary, and they have a right to withdraw at any time during the study. Refusal to sign or participate will not affect the patient's right to receive medical care. No study procedures will be done prior to obtaining informed consent.

Randomization and blinding

After obtaining a signed informed consent from the patient or the LAR, the patient will be randomly allocated 1:1 to Group S or Group R. Randomization will be performed by sealed envelopes available at the Shanghai Pulmonary Hospital. A researcher who will be masked will generate treatment assignments using a computer-generated random number list of variable block sizes (block size 4-6-8) by Stata 16.0 (STATACORP LLC.4905 Lake Way Drive). Randomization envelopes to be opened will be created by the research assistant just prior to when they are ready to randomize

a patient. The integrity and presence of the envelopes will be checked at each monitoring visit.

The research assistant (RA) who will be blinded to the randomized assignment of patients will conduct all baseline interviews. The patients will be blinded to their intervention as will the research staff completing the post-procedural follow-up questionnaire. It is not possible to blind anaesthesiologists involved in a patient's care, but bronchoscopists will be blinded.

Study treatment

Patients will fast prior to the procedure. After premedication with i.v. midazolam 0.02 mg/kg in the reception area, patients will be transferred to the operating theatre. Patients will be monitored with ECG, pulse oximetry, and non-invasive arterial pressure during the procedure and recovery period [until post-anaesthesia care unit (PACU) discharge]. All patients will receive oxygen application via a nasal tube with 2 liters of O_2/min initially. Once the plasma-site concentration (Cp) and effect-site concentration (Ce) has achieved equilibrium, a soft rubber type nasopharyngeal airway (No.6/7, Medis Medical, UK) will be inserted. The oxygen supply will be changed from nasal cannula to nasopharyngeal airway connected to an anaesthetic machine with 6 liters of O_2/min and an adjustable pressure-limiting (APL) valve setting of 30 cmH_2O. Both groups will be intravenously administered an initial loading dose of 0.8mcg/kg dexmedetomidine, followed by a maintenance dose of 0.5mcg/(kg·h) during the procedure. 4 mL of 1% lignocaine solution will be administered by nasopharyngeal airway to throat, then three aliquots of 4 mL of 1% lignocaine solution will be administered by endoscopist, one each to supraglottic, subglottic and carina through bronchoscope using the "spray as-you-go" technique[19]. A BF-260 electronic bronchoscope (BF-1T260/6C260, Olympus Corporation, Japan) will be used.

TCI plasma-site concentration (Cp) for sufentanil or remifentanil will be achieved using the Fresenius DPS workstation using the Gepts or Minto pharmacokinetic model respectively. The EC95 of sufentanil or remifentanil is set as the plasma target concentration and which is 0.212 ng/ml or 2.710 ng/ml respectively. Intravenous

injection of 10-20 mg propofol will be used as a remedy and repeatedly as necessary. The effective concentration (Ce) of sufentanil and remifentanil are based on our previous research using the biased coin up-and-down design sequential method. A MAP < 80% of baseline or 60 mmHg is regarded as hypotension. In the event hypotension happens, an intravenous injection of phenylephrine (25~100 mcg) will be administered as a rescue vasopressor.

Management of hypoxemia

Definition of hypoxemia: SpO_2 < 90% at any time [20]. The severity of hypoxemia is classified as follows: subclinical hypoxemia (SPO_2 of 90-95%), moderate hypoxemia (SPO_2 of 75-89%, ≤60 s), and severe hypoxemia (SpO_2 < 90% for >60 s or SpO_2 < 75% at any time)[21].

Once hypoxemia develops, it will be corrected using the following sequence: (1) patient stimulation, (2) increasing the volume of supplementary oxygen from 6 to 10 liters of O_2/min, (3) opening the airway using a jaw-thrust maneuver, (4) removing the bronchoscope tube and mask ventilation, and (5) laryngeal mask or tracheal intubation for mechanical ventilation.

Trial outcomes

Primary outcome

The primary outcome is the incidence of hypoxemia.

Secondary outcomes

1. Secondary outcome variables include the following：
2. The severity of hypoxemia.
3. Cough severity rated on a 4-point scale (no cough=1, slight coughing=2,moderate coughing = 3, severe coughing = 4). Coughing is considered slight if no more than 2 coughs in sequence occurred, moderate if 3-5 coughs in sequence occurred and severe if more than 5 coughs in sequence occurred.
4. Hemodynamic variables (blood pressure and heart rate).
5. Ramsay sedation scores during procedure.
6. Patient's comfort and tolerance to fiberscope assessed by Puchner comfort scale[22].

7. Recovery time.
8. Arterial blood gases (PO_2, PCO_2 and PH) before and after the operation.
9. The incidence of postoperative nausea and vomiting .
10. Satisfaction scores of the patient, bronchoscopist and anaesthesiologist.
11. The willingness of the patient to undergo repeat bronchoscopy.
12. Visual analog scale (VAS, 0-100mm) scores of sore throat at 30 min after the end of the operation.
13. Complications related to the procedure and anaesthesia.

Statistical methods

The analysis will be performed on an intention-to-treat basis, such that each patient is analyzed in the group to which he or she is randomized, regardless of actual compliance with the intended intervention. All the analyses will be conducted using Stata 16.0 (STATACORP LLC.4905 Lake Way Drive). A two-tailed p value equal or less than 0.05 will be considered as statistically significant. All tests, except for the primary outcome, will be exploratory. When individual items are missing from a scale, we will calculate the percent of missing items. If less than 10%, we will impute values using the mean of the remaining items. If more than 10%, the scale score will be missing, and unavailable for analysis.

Sample size calculation

Our previous study (unpublished) shows that the incidences of hypoxemia in the two groups are 10% (1/10) in sufentanil group and 27.27% (3/11) in remifentanil group. We determined that enrolment of 270 patients would provide a power of 90% to show a reduction in the rate of incidences of hypoxia between two groups at a two-sided alpha level of 0.05, accounting for 20% lost to follow-up.

Descriptive statistics

Continuous variables will be described using means and SD for normally distributed data. For continuous variables with non-normally distributed data, medians and ranges will be used. Categorical data will be described using counts, proportions, and risk ratios with 95% CIs.

Planned outcome analysis

Primary outcome

The incidences of hypoxia will be compared between the two groups using a χ2 test or an exact Fisher's exact test if required. The incidences of hypoxia will then be modelled (secondary analysis) using a multivariate logistic regression.

Secondary outcomes

Secondary endpoints will be compared between the two treatment groups by means of Student's t-test (or the Mann-Whitney U test, if necessary) for continuous quantitative variables and by means of the χ2 test (or Fisher's exact test) for qualitative variables. Linear models and logistics models will be used to compare the two groups in multivariate analyses. Time-to-event analyses will involve the Kaplan-Meier method and the Cox proportional hazards model.

DISCUSSION

MAC is a specific anaesthesia service performed by a qualified anaesthesia provider for a diagnostic or therapeutic procedure[23]. MAC is useful in patients who require repeated fiberoptic bronchoscopy as well as safe in respiratory depression when performed by experienced anaesthesiologists [24]. We will utilize MAC for patients with severe tracheal stenosis that requires fiberoptic bronchoscopy in this study.

TCI allows an accurate adaptation of the anaesthesia level and fewer overdose-linked adverse effects. As a decreased cumulative dose of sufentanil or remifentanil, hemodynamic stability, recovery and discharge may also be improved by using TCI. The Ce of sufentanil and remifentanil used in the study are based on our previous unpublished research.

This trial is the first randomized controlled study powered to test the hypothesis that sufentanil TCI compared with remifentanil TCI for MAC can reduce the incidence of hypoxemia and related adverse events in patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy. We believe that the findings of this study will have

significant clinical implications. This might mean that more studies are needed to determine the optimal strategies for anaesthesia management to prevent hypoxemia.

Data collection, monitoring and management

Preoperative, intraoperative and postoperative follow-up data will be collected from electronic medical records, monitoring machines and relevant manual records by the research staff (YJZ). All electronic and handwriting data will be stored on a password-protected computer. Data and safety monitoring will be the responsibility of the principle investigator (JML).

Trial status

The recruitment commenced in February 2021. It is anticipated that recruitment will end by June 2022. The version number of the protocol are v2.0.

Patient and public involvement

Patients or the public were not involved in the design of our research and will not be involved in conduct, reporting or dissemination of our research.

Dissemination policy

The results of this study will be disseminated regardless of the effect of the intervention on study outcomes. The manuscript describing the effect of the intervention will be submitted to a peer-reviewed journal when data collection and analyses are complete.

Contributors

WW and YZ designed the study, they are joint first author. WW and YJZ wrote the manuscript together. YZ provided substantial contributions to the conception and design of the study, wrote the statistical analysis plan and estimated the sample size. JML was responsible for designing the study and drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors gave their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

Funding

The study is funded by Shanghai Municipal Health Commission (Project

NO.201940366).

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Shanghai Pulmonary Hospital of China (approval No. K19-122). Informed consent must be obtained from all patients.

Patient consent for publication

Not required.

Competing interests

The authors declare that they have no competing interests.

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Figure 1
CONSORT flow diagram for the study. CONSORT, Consolidated Standards of Reporting Trials.

Figure 2
SPIRIT Figure-Schedule of enrolment, interventions, and assessments. SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

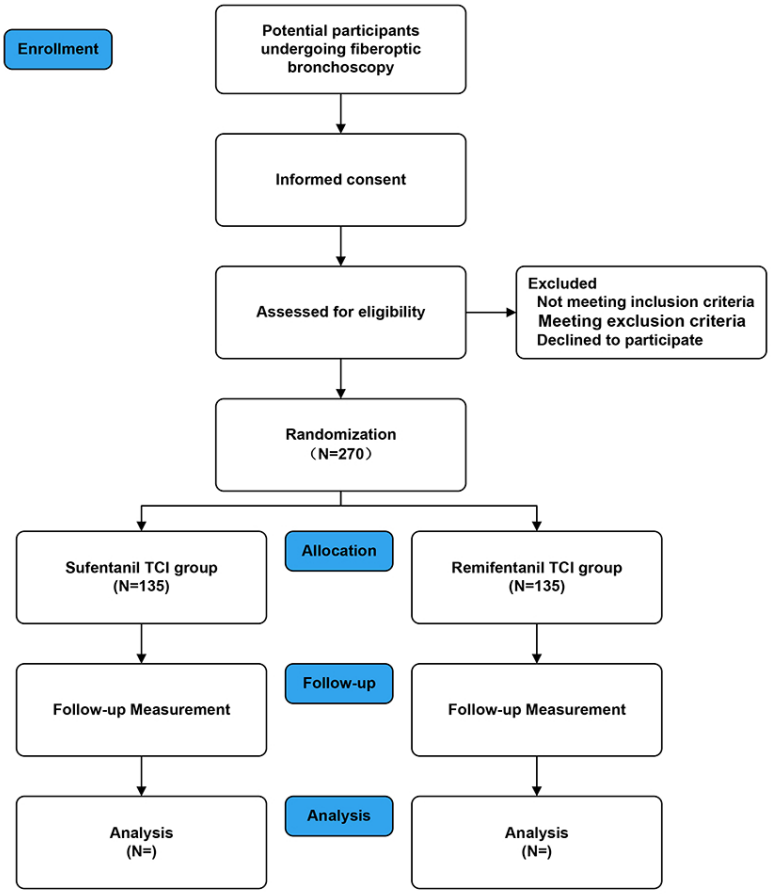

Figure 1.CONSORT flow diagram for the study. CONSORT, Consolidated Standards of Reporting Trials

STUDY PERIOD					
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT	t_{-1}	t_0	t_1	t_2	t_3
	Feb 2021-Jun 2022		During the procedure	PACU	
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Sufentanil TCI			X		
Remifentanil TCI			X		
ASSESSMENTS:					
Baseline variables	X	X			
Hypoxemia			X		
Cough severity			X		
Hemodynamic variables			X		
Sedation scores			X		
Patient's comfort			X		
Recovery time				X	
Postoperative nausea and vomiting				X	
Satisfaction				X	
Visual analog scale				X	

Figure 2. SPIRIT Figure-Schedule of enrolment, interventions, and assessments. SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	YES
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,10
	5b	Name and contact information for the trial sponsor	1,10
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-3
	6b	Explanation for choice of comparators	1-2
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4-5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variables (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5-6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5-6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5-6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8-9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8-9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9-10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9-10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2,10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	9-10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Translated ICFs can be provided on request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Sufentanil target controlled infusion (TCI) vs remifentanil TCI for monitored anaesthesia care for patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy: protocol for a prospective, randomized, controlled study

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Sufentanil target controlled infusion (TCI) vs remifentanil TCI for monitored anaesthesia care for patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy: protocol for a prospective, randomized, controlled study

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ABSTRACT

Introduction

The use of monitored anaesthesia care (MAC) is necessary and ubiquitous for fiberoptic bronchoscopy. Anesthetic management of patients with severe tracheal stenosis has always been a challenge. The efficacy and safety of the MAC with sufentanil target controlled infusion (TCI) and remifentanil TCI in patients with severe tracheal stenosis are still unknown.

Methods analysis

This study is a prospective, investigator-initiated, two-arm, randomized control trial to compare the efficacy and safety of sufentanil TCI with remifentanil TCI in patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy. 270 patients will be randomly assigned to the sufentanil TCI group or remifentanil TCI group, with a 1:1 ratio in two groups. The primary outcome is the incidence of hypoxemia (an oxygen saturation of <90%). The secondary outcome investigates the severity of hypoxemia, cough severity, hemodynamic variables, sedation scores and satisfaction scores.

Ethics and dissemination

The study has been approved by the Medical Ethics Committee of Shanghai Pulmonary Hospital. The results will be submitted for publication in peer-reviewed journals.

Trial registration number ChiCTR2100043380

Strengths and limitations of this study

- This study is an investigator-initiated, randomized, controlled trial, comparing two MAC strategies.
- This is the first prospective study of Anesthetic management of patients with severe tracheal stenosis during fiberoptic bronchoscopy.
- A homogeneous patient population with severe tracheal stenosis is included.
- The main limitation of our study is that considering the characteristics of the two MAC strategies, the overall trial is not double-blind.
- The analysis of the secondary objectives is explorative, due to sample size

restrictions.

INTRODUCTION

Since the introduction of the flexible fiberoptic bronchoscope, bronchoscopy has been widely used as a diagnostic tool in the field of clinical respiratory medicine. Approximately 500,000 fiberoptic bronchoscopy are performed in the United States annually[1]. Sedation is now generally recommended for all patients undergoing fiberoptic bronchoscopy unless a specific contraindication to sedation exists[2-4]. Sedation during fiberoptic bronchoscopy improves patient comfort and tolerance, and enhances the willingness to repeat the procedure, without increasing complications[3 5 6].

Bronchoscopy has been an integral part of the diagnosis and treatment of patients with severe tracheal stenosis[7]. Patients affected by severe tracheal stenosis develop symptoms such as stridor, dyspnea, voice changes, mucus production increasing, and persistent cough[8]. Most patients require sedation and analgesia to tolerate fiberoptic bronchoscopy. Anaesthetic management for patients with severe tracheal stenosis during fiberoptic bronchoscopy procedures has always been challenging, and there is no standardized practice currently[3 9].

Remifentanil has a rapid onset of action and elimination half-life and a predictable duration of action with no accumulation of effect on repeated dosing or with continuous infusion, which making it suitable for anaesthesia management of diagnostic and therapeutic bronchoscopy[10-15]. The degree of the noxious stimulation caused by the insertion and manipulation of a bronchoscope is often similar to a surgical incision. Remifentanil might cause respiratory depression or hemodynamic instability when effectively inhibiting operational stress, which is often very dangerous for patients with severe tracheal stenosis[14 16 17]. Sufentanil is a more potent opioid than remifentanil, its analgesic effect lasts longer and it is superior in terms of hemodynamic stability. Sufentanil has a longer half-time as compared with remifentanil, but TCI will prevent long-acting opioid-induced accumulation and allow rapid recovery from anaesthesia[18]. There have been no detailed investigations on the efficacy and safety of monitored anesthesia care (MAC) using sufentanil or remifentanil TCI in patients with severe

tracheal stenosis undergoing fiberoptic bronchoscopy. The aim of our study is to compare sufentanil TCI with remifentanil TCI in patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy.

Objectives

We aim to conduct a prospective randomized controlled trial comparing sufentanil TCI with remifentanil TCI and assume that sufentanil TCI would decrease the incidence of hypoxemia.

Primary objective

Determine the incidence of hypoxemia of MAC with sufentanil TCI versus MAC with remifentanil TCI in patients with severe tracheal stenosis undergoing bronchoscopy.

METHODS AND ANALYSIS

Study design

This is a single-center, randomized, investigator-initiated clinical trial of 270 patients with severe tracheal stenosis that requires fiberoptic bronchoscopy. The CONSORT flow chart is presented in Figure 1. A SPIRIT figure is included in Figure 2 with a checklist included as an additional document (Supplementary file 1). Patients will be randomly assigned to one of two groups. Group S will be received sufentanil TCI and Group R will be received remifentanil TCI.

Inclusion criteria

All patients treated with fiberoptic bronchoscopy in Shanghai Pulmonary Hospital will be screened for eligibility in strict accordance with the inclusion and exclusion criteria. Tracheal stenosis is defined as narrowing of the endotracheal lumen. The diagnosis will be determined by the same respiratory physician together with the same endoscopist. The inclusion criteria are patients aged 18–65 years, with the American Society of Anesthesiologists (ASA) physical status classifications I–III and Cotton-Myer grades II-III (the narrow of the endotracheal lumen is more than 50%). The exclusion criteria are shown in Table 1.

Table1. Summary of exclusion criteria of the trial.

Exclusion criteria
BMI>30 or < 18.5
Baseline oxygen desaturation (resting SpO_2 <90%)
Chronic opioid treatment, substance abuse or drug use
Pregnancy
History of allergy to related drugs
Severe coagulation dysfunction
Severe hepatic and renal dysfunction
Gastroesophageal reflux disease
History of abnormal recovery from anaesthesia
No informed consent
Patients with acute exacerbation of chronic obstructive pulmonary disease (COPD)

Recruitment

Consecutive patients who present to respiratory clinics at Shanghai Pulmonary Hospital with a diagnosis of tracheal stenosis and meet the inclusion criteria will be offered the opportunity to enroll in our study. We will inform them of details about our study. All patients will be provided with full information of their part in our study and assure that their information will be kept strictly confidential.

Information consent

Informed consent will be obtained from each patient or legally authorized representative (LAR) prior to enrollment in our study. This will provide a clear understanding that their participation is entirely voluntary, and they have a right to withdraw at any time during the study. Refusal to sign or participate will not affect the patient's right to receive medical care. No study procedures will be done prior to obtaining informed consent. A copy of the letter of information and consent is provided in Supplementary file 2.

Randomization and blinding

After obtaining a signed informed consent from the patient or the LAR, the patient will

be randomly allocated 1:1 to Group S or Group R. Randomization will be performed by sealed envelopes available at the Shanghai Pulmonary Hospital. A researcher who will be masked will generate treatment assignments using a computer-generated random number list of variable block sizes (block size 4-6-8) by Stata 16.0 (STATACORP LLC.4905 Lake Way Drive). Randomization envelopes to be opened will be created by the research assistant just prior to when they are ready to randomize a patient. The integrity and presence of the envelopes will be checked at each monitoring visit.

The research assistant (RA) who will be blinded to the randomized assignment of patients will conduct all baseline interviews. The patients will be blinded to their intervention as will the research staff completing the post-procedural follow-up questionnaire. It is not possible to blind anaesthesiologists involved in a patient's care, but bronchoscopists will be blinded.

Study treatment

Patients will fast prior to the procedure. After premedication with i.v. midazolam 0.02 mg/kg in the reception area, patients will be transferred to the operating theatre. Patients will be monitored with ECG, pulse oximetry, and non-invasive arterial pressure during the procedure and recovery period [until post-anaesthesia care unit (PACU) discharge]. All patients will receive oxygen application via a nasal tube with 2 liters of O_2/min initially. Once the plasma-site concentration (Cp) and effect-site concentration (Ce) has achieved equilibrium, a soft rubber type nasopharyngeal airway (No.6/7, Medis Medical, UK) will be inserted. The oxygen supply will be changed from nasal cannula to nasopharyngeal airway connected to an anaesthetic machine with 6 liters of O_2/min and an adjustable pressure-limiting (APL) valve setting of 30 cmH_2O. Both groups will be intravenously administered an initial loading dose of 0.8mcg/kg dexmedetomidine, followed by a maintenance dose of 0.5mcg/(kg·h) during the procedure. 4 mL of 1% lignocaine solution will be administered by nasopharyngeal airway to throat, then three aliquots of 4 mL of 1% lignocaine solution will be administered by endoscopist, one each to supraglottic, subglottic and carina

through bronchoscope using the "spray as-you-go" technique[19]. A BF-260 electronic bronchoscope (BF-1T260/6C260, Olympus Corporation, Japan) will be used. The airway will be fully assessed and the appropriate interventional procedure will be performed to relieve the obstruction and stabilize the airway. If biopsies are required, these specimens will be taken and sent for appropriate investigations. Procedures performed will involve debridement or coring out of the endoluminal lesion, balloon dilation, serial mechanical dilation with tapering, cryotherapy, variously sized dilators, laser disobliteration, or airway stenting.

TCI plasma-site concentration (Cp) for sufentanil or remifentanil will be achieved using the Fresenius DPS workstation using the Gepts or Minto pharmacokinetic model respectively. The EC95 of sufentanil or remifentanil is set as the plasma target concentration and which is 0.212 ng/ml or 2.710 ng/ml respectively. Intravenous injection of 10-20 mg propofol will be used as a remedy and repeatedly as necessary. The effective concentration (Ce) of sufentanil and remifentanil are based on our previous research using the biased coin up-and-down design sequential method. A MAP < 80% of baseline or 60 mmHg is regarded as hypotension. In the event hypotension happens, an intravenous injection of phenylephrine (25~100 mcg) will be administered as a rescue vasopressor.

Management of hypoxemia

Definition of hypoxemia: SpO_2 < 90% at any time [20]. The severity of hypoxemia is classified as follows: subclinical hypoxemia (SPO_2 of 90-95%), moderate hypoxemia (SPO_2 of 75-89%, ≤60 s), and severe hypoxemia (SpO_2 < 90% for >60 s or SpO_2 < 75% at any time)[21].

Once hypoxemia develops, it will be corrected using the following sequence: (1) patient stimulation, (2) increasing the volume of supplementary oxygen from 6 to 10 liters of O_2/min, (3) opening the airway using a jaw-thrust maneuver, (4) removing the bronchoscope tube and mask ventilation, and (5) laryngeal mask or tracheal intubation for mechanical ventilation.

Trial outcomes

Primary outcome

The primary outcome is the incidence of hypoxemia.

Secondary outcomes

Secondary outcome variables include the following：

1. The severity of hypoxemia.
2. Cough severity rated on a 4-point scale (no cough=1, slight coughing=2,moderate coughing = 3, severe coughing = 4). Coughing is considered slight if no more than 2 coughs in sequence occurred, moderate if 3-5 coughs in sequence occurred and severe if more than 5 coughs in sequence occurred.
3. Hemodynamic variables (blood pressure and heart rate).
4. Modified Ramsay sedation scores during procedure.
5. Patient's comfort and tolerance to fiberscope assessed by Puchner comfort scale[22].
6. Recovery time.
7. Arterial blood gases (PO_2, PCO_2 and PH) before and after the operation.
8. The incidence of postoperative nausea and vomiting .
9. Satisfaction scores of the patient, bronchoscopist and anaesthesiologist.
10. The willingness of the patient to undergo repeat bronchoscopy.
11. Visual analog scale (VAS, 0-100mm) scores of sore throat at 30 min after the end of the operation.
12. Complications related to the procedure and anaesthesia.

Statistical methods

The analysis will be performed on an intention-to-treat basis, such that each patient is analyzed in the group to which he or she is randomized, regardless of actual compliance with the intended intervention. All the analyses will be conducted using Stata 16.0 (STATACORP LLC.4905 Lake Way Drive). A two-tailed p value equal or less than 0.05 will be considered as statistically significant. All tests, except for the primary outcome, will be exploratory. When individual items are missing from a scale, we will calculate the percent of missing items. If less than 10%, we will impute values

using the mean of the remaining items. If more than 10%, the scale score will be missing, and unavailable for analysis.

Sample size calculation

Our previous study (unpublished) shows that the incidences of hypoxemia in the two groups are 10% (1/10) in sufentanil group and 27.27% (3/11) in remifentanil group. We determined that enrolment of 270 patients would provide a power of 90% to show a reduction in the rate of incidences of hypoxia between two groups at a two-sided alpha level of 0.05, accounting for 20% lost to follow-up.

Descriptive statistics

Continuous variables will be described using means and SD for normally distributed data. For continuous variables with non-normally distributed data, medians and ranges will be used. Categorical data will be described using counts, proportions, and risk ratios with 95% CIs.

Planned outcome analysis

Primary outcome

The incidences of hypoxia will be compared between the two groups using a χ2 test or an exact Fisher's exact test if required. The incidences of hypoxia will then be modelled (secondary analysis) using a multivariate logistic regression.

Secondary outcomes

Secondary endpoints will be compared between the two treatment groups by means of Student's t-test (or the Mann-Whitney U test, if necessary) for continuous quantitative variables and by means of the χ2 test (or Fisher's exact test) for qualitative variables. Linear models and logistics models will be used to compare the two groups in multivariate analyses. Time-to-event analyses will involve the Kaplan-Meier method and the Cox proportional hazards model.

DISCUSSION

MAC is a specific anaesthesia service performed by a qualified anaesthesia provider for a diagnostic or therapeutic procedure[23]. MAC is useful in patients who require

repeated fiberoptic bronchoscopy as well as safe in respiratory depression when performed by experienced anaesthesiologists [24]. We will utilize MAC for patients with severe tracheal stenosis that requires fiberoptic bronchoscopy in this study.

TCI allows an accurate adaptation of the anaesthesia level and fewer overdose-linked adverse effects. As a decreased cumulative dose of sufentanil or remifentanil, hemodynamic stability, recovery and discharge may also be improved by using TCI. The Ce of sufentanil and remifentanil used in the study are based on our previous unpublished research.

This trial is the first randomized controlled study powered to test the hypothesis that sufentanil TCI compared with remifentanil TCI for MAC can reduce the incidence of hypoxemia and related adverse events in patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy. We believe that the findings of this study will have significant clinical implications. This might mean that more studies are needed to determine the optimal strategies for anaesthesia management to prevent hypoxemia.

Data collection, monitoring and management

Preoperative, intraoperative and postoperative follow-up data will be collected from electronic medical records, monitoring machines and relevant manual records by the research staff (YJZ). All electronic and handwriting data will be stored on a password-protected computer. Data will be recorded on a standardised paper form (Supplementary file 3) and subsequently double-entered using Epidata software v3.1 by two trained research assistants. Data and safety monitoring will be the responsibility of the principle investigator (JML).

Trial status

The recruitment commenced in February 2021. It is anticipated that recruitment will end by June 2023. The version number of the protocol are v3.0.

Patient and public involvement

Patients or the public were not involved in the design of our research and will not be involved in conduct, reporting or dissemination of our research.

Dissemination policy

The results of this study will be disseminated regardless of the effect of the intervention on study outcomes. The manuscript describing the effect of the intervention will be submitted to a peer-reviewed journal when data collection and analyses are complete.

Contributors

WW and YZ designed the study, they are joint first author. WW and YJZ wrote the manuscript together. YZ provided substantial contributions to the conception and design of the study, wrote the statistical analysis plan and estimated the sample size. JML was responsible for designing the study and drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors gave their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

Funding

The study is funded by Shanghai Municipal Health Commission (Project NO.201940366).

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Shanghai Pulmonary Hospital of China (approval No. K19-122). Informed consent must be obtained from all patients.

Patient consent for publication

Not required.

Competing interests

The authors declare that they have no competing interests.

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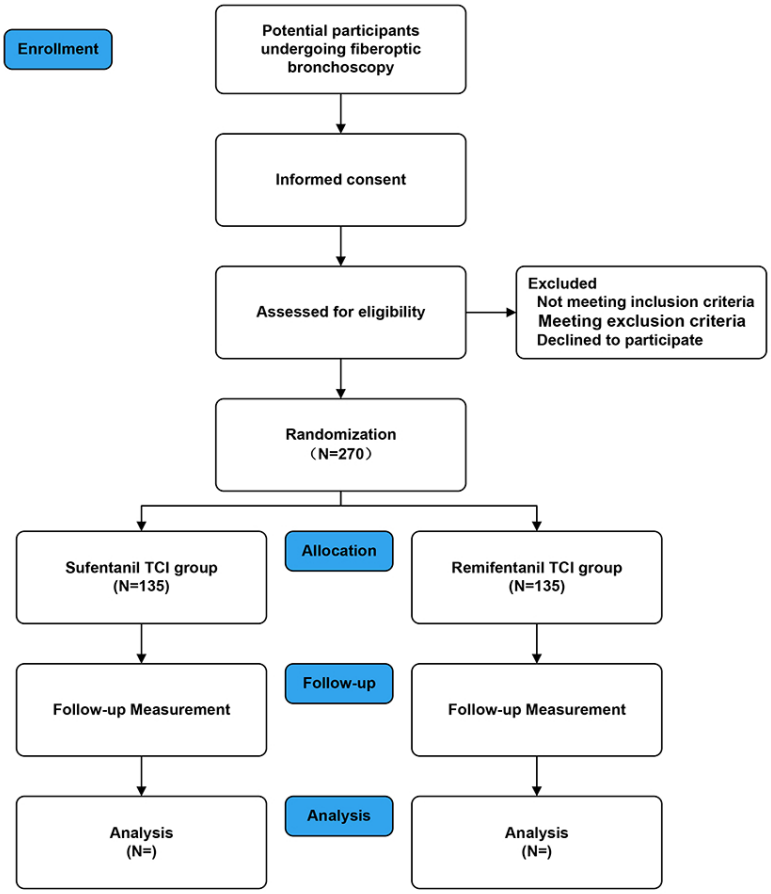
Figure 1
CONSORT flow diagram for the study. CONSORT, Consolidated Standards of Reporting Trials.

Figure 2
SPIRIT Figure-Schedule of enrolment, interventions, and assessments. SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.



CONSORT flow diagram for the study. CONSORT, Consolidated Standards of Reporting Trials.

STUDY PERIOD					
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT	t_{-1}	t_0	t_1	t_2	t_3
	Feb 2021-Jun 2022		During the procedure	PACU	
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Sufentanil TCI			X		
Remifentanil TCI			X		
ASSESSMENTS:					
Baseline variables	X	X			
Hypoxemia			X		
Cough severity			X		
Hemodynamic variables			X		
Sedation scores			X		
Patient's comfort			X		
Recovery time				X	
Postoperative nausea and vomiting				X	
Satisfaction				X	
Visual analog scale				X	

SPIRIT Figure-Schedule of enrolment, interventions, and assessments. SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	YES
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,10
	5b	Name and contact information for the trial sponsor	1,10
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	10
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1-3
	6b	Explanation for choice of comparators	1-2
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4-5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variables (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5-6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5-6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5-6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8-9
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8-9
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9-10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9-10
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2,10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	9-10

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	10
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	10
	31b	Authorship eligibility guidelines and any intended use of professional writers	10
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Translated ICFs can be provided on request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Practice name:
Participant ID:

Informed Consent

Informed Consent form for patient.

This Informed Consent Form is for men and women who attend Shanghai Pulmonary Hospital and who we are inviting to participate in research on anesthesia for bronchoscopy.

The title of our research project is: *Sufentanil target controlled infusion (TCI) vs remifentanil TCI for monitored anaesthesia care for patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy*.

Principal Investigator: Jianming Liu, MD
Organization: Department of Anaesthesiology, Shanghai Pulmonary Hospital, Tongji University School of Medicine

This Informed Consent Form has two parts:

1. Information Sheet (to share information about the research with you)
2. Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

PART 1: Information Sheet

Introduction

I am Jianming Liu, working for department of Anaesthesiology. We are doing research on monitored anaesthesia care for patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy. I am going to give you information and invite you to be part of this research.

You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research. There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.)

Purpose of the research

Bronchoscopy has been an integral part of the diagnosis and treatment of patients with tracheal stenosis. The two opioids most commonly used are sufentanil and remifentanil. We aim to conduct a trial comparing sufentanil with remifentanil in patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy.

Participant selection

We are inviting all adults with severe tracheal stenosis attend Shanghai Pulmonary Hospital to participate in the research.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will offer the treatment that is routinely offered, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.

Procedures and Protocol

Participants will be randomly assigned to one of two groups. Participants in one group will be given monitored anesthesia care (MAC) using sufentanil target controlled infusion. Participants in the other group will be given monitored anesthesia care (MAC) using remifentanil. We will then compare which of the two has the best results. The healthcare workers will be looking after you and the other participants very carefully during the study. If we are concerned about what the treatment is doing, we will find out which treatment you

are getting and make changes. If there is anything you are concerned about or that is bothering you about the research please talk to me or one of the other researchers.

For any clinical study (if relevant):

We will take arterial blood from your arm using a syringe through arterial line. This blood taken is painless. In total, we will take about 2 samples of 1 ml arterial blood. At

the end of the research any left-over blood sample will be destroyed).

Description of the Process

In the first time, a small amount of blood, equal to about a teaspoon, will be taken from your arm with a syringe through arterial catheter. This blood will be tested with a blood analyzer. We will ask you a few questions about your general health.

You'll be anesthetized during fiberoptic bronchoscopy. After treatment we'll draw your blood and also ask you a few questions.

Duration

The research takes place over 1/2 days.

Risks

Any risk can appear during the process. Mechanical complications of fiberoptic bronchoscopy include nasopharyngeal, vocal cord, and airway trauma as well as bronchospasm, laryngospasm, pulmonary derecruitment/atelectasis, pneumothorax, airway hemorrhage, and introduction or exacerbation of infection. Systemic complications are primarily related to the procedure itself, medication administration, or patient comorbidities. The healthcare workers will be looking after you and the other participants very carefully during the study. If we are concerned about what the treatment is doing, we will find out which treatment you are getting and make changes.

Benefits

If you participate in this research, you will have the following benefits: any interim illnesses will be treated at no charge to you. The Fresenius DPS workstation for TCI used for free. Your participation is likely to help us find the answer to the research question.

Reimbursements

Your participation is free. You will not be given any other money or gifts to take part in this research.

Confidentiality

With this research, something out of the ordinary is being done in your community. It is possible that if others in the community are aware that you are participating, they may ask you questions. We will not be sharing the identity of those participating in the research.

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except [Yi Zhou and Jianming Liu) who will have access to the information.

Sharing the Results

The knowledge that we get from doing this research will be shared with you through community meetings before it is made widely available to the public. Confidential information will not be shared. After these meetings, we will publish the results in order that other interested people may learn from our research.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.

Alternatives to Participating

If you do not wish to take part in the research, you will be provided with the established standard treatment available at our hospital.

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:
DR. Jianming Liu, Phone: 86-18019285297
This proposal has been reviewed and approved by the Ethics Committee of Shanghai Pulmonary Hospital of China (approval No. K19-122) which is a committee whose task it is to make sure that research participants are protected from harm.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

PART 2: Certificate of Consent

This section should be written in the first person and have a statement similar to the one in bold below. If the participant is illiterate but gives oral consent, a witness or a legally authorized representative must sign. A researcher or the person going over the informed consent must sign each consent. The understanding should perhaps be better tested through targeted questions during the reading of the information sheet (some examples of questions are given above), or through the questions being asked at the end of the reading of the information sheet, if the potential participant is reading the information sheet him/herself.

		Please initial each box
1	I have read the foregoing information, or it has been read to me.	☐
2	I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction.	☐
3	I consent voluntarily to participate as a participant in this research.	☐

Print Name of Participant _____

Signature of Participant _____

Date(Day/month/year) _____

If illiterate

Aliterate witness or legally authorized representative must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.

		Please initial each box
1	I have witnessed the accurate reading of the consent form to the potential participant	☐
2	I have witnessed the individual has had the opportunity to ask questions.	☐
3	I confirm that the individual has given consent freely.	☐

Print Name of witness or legally authorized representative _____

Signature of witness or legally authorized representative _____

Date(Day/month/year) _____

Thumb print of participant ☐

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher _____

Signature of Researcher _____

Date(Day/month/year) _____

Protocol No:	P20200828V3		
Site	☐☐	**Subject ID:**	☐☐☐
Randomisation No:	☐☐	**Subject Initials:**	☐☐☐☐
Investigator Identifier:	☐☐☐		

Case Report Form

Sufentanil target controlled infusion (TCI) vs remifentanil TCI for monitored anaesthesia care for patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy

By

Shanghai Pulmonary Hospital

Inclusion Criteria

Subjects who meet the following criteria may be included in the study. Did the subject meet the following criteria requirements for inclusion? (√ Yes or No)		Yes 1	No* 2
01	Cotton-Myer grades II-III		
02	Aged 18–65 years		
03	ASA I-III		

* If No, document on Subject Eligibility Page.

Exclusion Criteria

The following will exclude potential subjects from the study. Does the subject have any of the following? (√ Yes or No)		Yes* 1	No 2
01	BMI>30 or < 18.5		
02	Baseline oxygen desaturation (resting SpO_2 <90%)		
03	Pregnancy		
04	History of allergy to related drugs		
05	Severe coagulation dysfunction		
06	Severe hepatic and renal dysfunction		
07	Gastroesophageal reflux disease		
08	History of abnormal recovery from anaesthesia		
09	No informed consent		

*If Yes, document on Subject Eligibility Page

Information Session

Date of Information Session	Did the subject attend the Information Session?	Comments
_____/_____/_____ DD / MM / YY	1 ☐Yes 2 ☐No（explain, if No）	

Subject Eligibility

Date the Subject Signed the Informed Consent Form:	_____/_____/_____ DD / MM / YY
Did the subject meet all of the inclusion/exclusion criteria?	1☐Yes 2☐No

If the subject did not meet all of the Inclusion/Exclusion criteria, provide criterion number and explanation below.

Category	Inclusion/ Exclusion No.	Explanation	Exemption Granted?	If Yes, Date Granted DD/MM/YYYY
1☐Inclusion 2☐Exclusion			1☐Yes 2☐No	___/___/___
1☐Inclusion 2☐Exclusion			1☐Yes 2☐No	___/___/___
1☐Inclusion 2☐Exclusion			1☐Yes 2☐No	___/___/___

Demographics

Date DD/MM/YYYY	Date of Birth DD/MM/YYYY	Gender	Ethnicity
☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	1☐Male	1☐Han
		2☐Female	2☐Non-han
Body Measurements			
Were Body Measurements Collected?		Date DD/MM/YYYY	
1☐Yes 2☐No		☐☐/☐☐/☐☐☐☐	
Parameter	Unit	Result	
Height	cm	☐☐☐	
Weight	Kg	☐☐☐	
Vital Signs			
Were Body Measurements Collected?		Date	
1☐Yes 2☐No		☐☐/☐☐/☐☐☐☐	
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Body Temperature	°C	☐☐.☐	
12-Lead Electrocardiogram Report			
Was ECG performed?		Date DD/MM/YYYY	Actual Time 24-hour clock
1☐Yes 2☐No		☐☐/☐☐/☐☐☐☐	☐☐:☐☐
ECG Interpretation:	1☐Normal	2☐Abnormal, NCS	3☐Abnormal
Comments Regarding CS Findings:			

Medical History

Does the subject have any relevant medical history?		Date DD/MM/YYYY	
1☐Yes 2☐No		____/____/_____	
Diagnosis/Procedure	Date of Onset DD/MM/YYYY	Date of Resolution DD/MM/YYYY	
1	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
2	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
3	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
4	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
5	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
6	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
7	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
8	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
9	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING

Laboratory Analysis

Parameter	Unit	Result
SPO_2		☐☐☐
Arterial blood gas analysis		
PH		☐.☐☐
$PaCO_2$	mmHg	☐☐☐
PaO_2	mmHg	☐☐☐
HCO_3	mEq/L	☐☐

Intervention Phase

Date DD/MM/YYYY	____/____/____			
Group	1☐Group R		2☐Group S	
Whether or not hypoxemia occurs				
1☐subclinical hypoxemia (SPO2 of 90-95%),	2☐moderate hypoxemia (SPO2 of 75-89%, ≤60 s		3☐severe hypoxemia (SpO2 < 90% for >60 s or SpO2 < 75% at any time)	
Management of hypoxemia				
1☐patient stimulation	2☐increasing the volume of supplementary oxygen	3☐jaw-thrust maneuver	4☐mask ventilation	5☐ mechanical ventilation.
Puchner five-point fiber-optic intubation comfort scale				
1☐No reaction	2☐Slight grimacing	3☐Heavy grimacing	4☐Verbal objection	5☐Defensive movement

T0	10 minutes after entering the operation room	
Parameter	Unit	Result
Systolic Blood Pressure	mmHg	☐☐☐
Diastolic Blood Pressure	mmHg	☐☐☐
Heart Rate	beats/minute	☐☐☐
Respiratory Rate	breaths/minute	☐☐
Spo2		☐☐☐

T1	Cp and Ce has achieved equilibrium		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐

	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T2	When bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T3	1 minute after bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T4	5 minutes after bronchoscope is inserted	
Parameter	Unit	Result
Systolic Blood Pressure	mmHg	☐☐☐

Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T5	10 minutes after bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T6	15 minutes after bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐

	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T6	20 minutes after bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T7	25 minutes after bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T8	30 minutes after bronchoscope is inserted	
Parameter	Unit	Result
Systolic Blood Pressure	mmHg	☐☐☐

Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T9	60 minutes after bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

Type of fiberoptic bronchoscopy procedure				
1☐Diagnostic		2☐Therapeutic		
If it is Therapeutic bronchoscopy				
1☐Injection of medication	2☐Endotherm knife	3☐Cryotherapy		
4☐Laser	5☐Stent			
Operation time	☐☐☐☐	min	Endoscopist	☐☐☐
Satisfaction scores of bronchoscopist	1☐	2☐	3☐	
	4☐	5☐		
Satisfaction scores of anaesthesiologist	1☐	2☐	3☐	
	4☐	5☐		

Vasoactive drugs used			
Whether or not vasoactive drugs are used	1☐Yes	2☐No	
Vasoactive drug type	name	dosage	whether it is effective or not
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents		1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents		1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents		1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents		1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents		1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents		1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents		1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No

Post Intervention Phase

Recovery time	☐☐☐	min		
Whether nausea and vomiting occur				
1☐Yes	2☐No			
Assessment of PONV				
1☐Mild	2☐moderate	3☐severe		
Satisfaction scores of the patient				
1☐	2☐	3☐	4☐	5☐
willingness of the patient to undergo repeat bronchoscopy.				
1☐Not at all likely	2☐1–3	3☐4–6	4☐7–9	5☐ Extremely likely (10)
VAS scores of sore throat				
1☐	2☐	3☐	4☐	5☐
6☐	7☐	8☐	9☐	10☐
T10	At PACU			
Parameter	Unit	Result		
Systolic Blood Pressure	mmHg	☐☐☐		
Diastolic Blood Pressure	mmHg	☐☐☐		
Heart Rate	beats/minute	☐☐☐		
Respiratory Rate	breaths/minute	☐☐		
Spo2		☐☐☐		
Ramsay Sedation Scale	1☐	2☐	3☐	
	4☐	5☐	6☐	
	7☐	8☐		
Cough	1☐	2☐	3☐	4☐
Arterial blood gas analysis				
PH		☐.☐☐		
$PaCO_2$	mmHg	☐☐☐		
PaO_2	mmHg	☐☐☐		
HCO_3	mEq/L	☐☐		

Adverse Event information

Whether adverse events occurred		
1□Yes	2□No	
Whether serious adverse events occurred		
1□Yes	2□No	
Describe the AE and the connection to project procedures		
AE onset date	□□/□□/□□□□	DD/MM/YYYY
AE stop date	□□/□□/□□□□	DD/MM/YYYY
Date of AE awareness	□□/□□/□□□□	DD/MM/YYYY
Severity		
1□mild	2□moderate	3□severe
Outcome		
1□recovered/resolved	2□recovered/resolved with sequelae	3□study participant died
4□continuing	5□unknown	6□other
SAE causality		
1□Not related	2□Unlikely	3□Possibly
4□Probably	5□Definitely	
Describe the AE and the connection to project procedures		
AE onset date	□□/□□/□□□□	DD/MM/YYYY
AE stop date	□□/□□/□□□□	DD/MM/YYYY
Date of AE awareness	□□/□□/□□□□	DD/MM/YYYY
Severity		
1□mild	2□moderate	3□severe
Outcome		
1□recovered/resolved	2□recovered/resolved with sequelae	3□study participant died

4□continuing	5□unknown	6□other
SAE causality		
1□Not related	2□Unlikely	3□Possibly
4□Probably	5□Definitely	
Describe the AE and the connection to project procedures		
AE onset date	□□/□□/□□□□	DD/MM/YYYY
AE stop date	□□/□□/□□□□	DD/MM/YYYY
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Sufentanil target controlled infusion (TCI) vs remifentanil TCI for monitored anaesthesia care for patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy: protocol for a prospective, randomized, controlled study

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Primary Subject Heading:	Anaesthesia
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Keywords:	Adult anaesthesia < ANAESTHETICS, Endoscopic surgery < OTOLARYNGOLOGY, Bronchoscopy < THORACIC MEDICINE, Chronic airways disease < THORACIC MEDICINE, Respiratory tract tumours < THORACIC MEDICINE

Sufentanil target controlled infusion (TCI) vs remifentanil TCI for monitored anaesthesia care for patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy: protocol for a prospective, randomized, controlled study

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ABSTRACT

Introduction

The use of monitored anaesthesia care (MAC) is necessary and ubiquitous for fiberoptic bronchoscopy. Anesthetic management of patients with severe tracheal stenosis has always been a challenge. The efficacy and safety of the MAC with sufentanil target controlled infusion (TCI) and remifentanil TCI in patients with severe tracheal stenosis are still unknown.

Methods analysis

This study is a prospective, investigator-initiated, two-arm, randomized control trial to compare the efficacy and safety of sufentanil TCI with remifentanil TCI in patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy. 270 patients will be randomly assigned to the sufentanil TCI group or remifentanil TCI group, with a 1:1 ratio in two groups. The primary outcome is the incidence of hypoxemia (an oxygen saturation of <90%). The secondary outcome investigates the severity of hypoxemia, cough severity, hemodynamic variables, sedation scores and satisfaction scores.

Ethics and dissemination

The study has been approved by the Medical Ethics Committee of Shanghai Pulmonary Hospital (approval No. K19-122). The results will be submitted for publication in peer-reviewed journals.

Trial registration number ChiCTR2100043380

Strengths and limitations of this study

- This study is an investigator-initiated, randomized, controlled trial, comparing two MAC strategies.
- This is the first prospective study of anesthetic management of patients with severe tracheal stenosis during fiberoptic bronchoscopy.
- A homogeneous patient population with severe tracheal stenosis is included.
- The main limitation of our study is that considering the characteristics of the two MAC strategies, the overall trial is not double-blind.
- The analysis of the secondary objectives is explorative, due to sample size

restrictions.

INTRODUCTION

Since the introduction of the flexible fiberoptic bronchoscope, bronchoscopy has been widely used as a diagnostic tool in the field of clinical respiratory medicine. Approximately 500,000 fiberoptic bronchoscopy are performed in the United States annually[1]. Sedation is now generally recommended for all patients undergoing fiberoptic bronchoscopy unless a specific contraindication to sedation exists[2-4]. Sedation during fiberoptic bronchoscopy improves patient comfort and tolerance and enhances the willingness to repeat the procedure, without increasing complications[3 5 6].

Bronchoscopy has been an integral part of the diagnosis and treatment of patients with severe tracheal stenosis[7]. Patients affected by severe tracheal stenosis develop symptoms such as stridor, dyspnea, voice changes, increased mucus production, and persistent cough[8]. Most patients require sedation and analgesia to tolerate fiberoptic bronchoscopy. Anaesthetic management for patients with severe tracheal stenosis during fiberoptic bronchoscopy procedures has always been challenging, and there is no standardized practice currently[3 9].

Remifentanil has a rapid onset of action and elimination half-life and a predictable duration of action with no accumulation of effect on repeated dosing or with continuous infusion, which making it suitable for anaesthesia management of diagnostic and therapeutic bronchoscopy[10-15]. The degree of the noxious stimulation caused by the insertion and manipulation of a bronchoscope is often similar to a surgical incision. Remifentanil might cause respiratory depression or hemodynamic instability when effectively inhibiting operational stress, which is often very dangerous for patients with severe tracheal stenosis[14 16 17]. Sufentanil is a more potent opioid than remifentanil, its analgesic effect lasts longer and it is superior in terms of hemodynamic stability. Sufentanil has a longer half-time as compared with remifentanil, but TCI will prevent long-acting opioid-induced accumulation and allow rapid recovery from anaesthesia[18]. There have been no detailed investigations on the efficacy and safety of monitored anesthesia care (MAC) using sufentanil or remifentanil TCI in patients with severe

tracheal stenosis undergoing fiberoptic bronchoscopy. The aim of our study is to compare sufentanil TCI with remifentanil TCI in patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy.

Objectives

We aim to conduct a prospective randomized controlled trial comparing sufentanil TCI with remifentanil TCI and assume that sufentanil TCI would decrease the incidence of hypoxemia.

Primary objective

Determine the incidence of hypoxemia of MAC with sufentanil TCI versus MAC with remifentanil TCI in patients with severe tracheal stenosis undergoing bronchoscopy.

METHODS AND ANALYSIS

Study design

This is a single-center, randomized, investigator-initiated clinical trial of 270 patients with severe tracheal stenosis that requires fiberoptic bronchoscopy. The CONSORT flow chart is presented in Figure 1. A SPIRIT figure is included in Figure 2 with a checklist included as an additional document (Supplementary file 1). Patients will be randomly assigned to one of two groups. Group S will be received sufentanil TCI and Group R will be received remifentanil TCI.

Inclusion criteria

All patients treated with fiberoptic bronchoscopy in Shanghai Pulmonary Hospital will be screened for eligibility in strict accordance with the inclusion and exclusion criteria. Tracheal stenosis is defined as narrowing of the endotracheal lumen. The diagnosis will be determined by the same respiratory physician together with the same endoscopist. The inclusion criteria are patients aged 18–65 years, with the American Society of Anesthesiologists (ASA) physical status classifications I–III and Cotton-Myer grades II-III (the narrow of the endotracheal lumen is more than 50%). The exclusion criteria are shown in Table 1.

Table1. Summary of exclusion criteria of the trial.

Exclusion criteria
BMI>30 or < 18.5
Baseline oxygen desaturation (resting SpO_2 <90%)
Chronic opioid treatment, substance abuse or drug use
Pregnancy
History of allergy to related drugs
Severe coagulation dysfunction
Severe hepatic and renal dysfunction
Gastroesophageal reflux disease
History of abnormal recovery from anaesthesia
No informed consent
Patients with acute exacerbation of chronic obstructive pulmonary disease (COPD)

Recruitment

Consecutive patients who present to respiratory clinics at Shanghai Pulmonary Hospital with a diagnosis of tracheal stenosis and meet the inclusion criteria will be offered the opportunity to enroll in our study. We will inform them of details about our study. All patients will be provided with full information of their part in our study and assure that their information will be kept strictly confidential.

Information consent

Informed consent will be obtained from each patient or legally authorized representative (LAR) prior to enrollment in our study. This will provide a clear understanding that their participation is entirely voluntary, and they have a right to withdraw at any time during the study. Refusal to sign or participate will not affect the patient's right to receive medical care. No study procedures will be done prior to obtaining informed consent. A copy of the letter of information and consent is provided in Supplementary file 2.

Randomization and blinding

After obtaining a signed informed consent from the patient or the LAR, the patient will

be randomly allocated 1:1 to Group S or Group R. Randomization will be performed by sealed envelopes available at the Shanghai Pulmonary Hospital. A masked researcher will generate treatment assignments using a computer-generated random number list of variable block sizes (block size 4-6-8) by Stata 16.0 (STATACORP LLC.4905 Lake Way Drive). Randomization envelopes to be opened will be created by the research assistant just prior to when they are ready to randomize a patient. The integrity and presence of the envelopes will be checked at each monitoring visit.

The research assistant (RA) who will be blinded to the randomized assignment of patients will conduct all baseline interviews. The patients will be blinded to their intervention as will the research staff completing the post-procedural follow-up questionnaire. It is not possible to blind anaesthesiologists involved in a patient's care, but bronchoscopists will be blinded.

Study treatment

Patients will fast prior to the procedure. After premedication with i.v. midazolam 0.02 mg/kg in the reception area, patients will be transferred to the operating theatre. Patients will be monitored with ECG, pulse oximetry, and non-invasive arterial pressure during the procedure and recovery period [until post-anaesthesia care unit (PACU) discharge]. All patients will receive oxygen application via a nasal tube with 2 liters of O_2/min initially. Once the plasma-site concentration (Cp) and effect-site concentration (Ce) has achieved equilibrium, a soft rubber type nasopharyngeal airway (No.6/7, Medis Medical, UK) will be inserted. The oxygen supply will be changed from nasal cannula to nasopharyngeal airway connected to an anaesthetic machine with 6 liters of O_2/min and an adjustable pressure-limiting (APL) valve setting of 30 cmH_2O. Both groups will be intravenously administered an initial loading dose of 0.8mcg/kg dexmedetomidine, followed by a maintenance dose of 0.5mcg/(kg·h) during the procedure. 4 mL of 1% lignocaine solution will be administered by nasopharyngeal airway to throat, then three aliquots of 4 mL of 1% lignocaine solution will be administered by endoscopist, one each to supraglottic, subglottic and carina through bronchoscope using the "spray as-you-go" technique[19]. A BF-260 electronic

bronchoscope (BF-1T260/6C260, Olympus Corporation, Japan) will be used. The airway will be fully assessed and the appropriate interventional procedure will be performed to relieve the obstruction and stabilize the airway. If biopsies are required, these specimens will be taken and sent for appropriate investigations. Procedures performed will involve debridement or coring out of the endoluminal lesion, balloon dilation, serial mechanical dilation with tapering, cryotherapy, variously sized dilators, laser disobliteration, or airway stenting.

TCI plasma-site concentration (Cp) for sufentanil or remifentanil will be achieved using the Fresenius DPS workstation using the Gepts or Minto pharmacokinetic model respectively. The EC95 of sufentanil or remifentanil is set as the plasma target concentration and which is 0.212 ng/ml or 2.710 ng/ml respectively. Intravenous injection of 10-20 mg propofol will be used as a remedy and repeatedly as necessary. The effective concentration (Ce) of sufentanil and remifentanil are based on our previous research using the biased coin up-and-down design sequential method. A MAP < 80% of baseline or 60 mmHg is regarded as hypotension. In the event hypotension happens, an intravenous injection of phenylephrine (25~100 mcg) will be administered as a rescue vasopressor.

Management of hypoxemia

Definition of hypoxemia: SpO_2 < 90% at any time [20]. The severity of hypoxemia is classified as follows: subclinical hypoxemia (SPO_2 of 90-95%), moderate hypoxemia (SPO_2 of 75-89%, ≤60 s), and severe hypoxemia (SpO_2 < 90% for >60 s or SpO_2 < 75% at any time)[21].

Once hypoxemia develops, it will be corrected using the following sequence: (1) patient stimulation, (2) increasing the volume of supplementary oxygen from 6 to 10 liters of O_2/min, (3) opening the airway using a jaw-thrust maneuver, (4) removing the bronchoscope tube and mask ventilation, and (5) laryngeal mask or tracheal intubation for mechanical ventilation.

Trial outcomes

Primary outcome

The primary outcome is the incidence of hypoxemia.

Secondary outcomes

Secondary outcome variables include the following：

1. The severity of hypoxemia.
2. Cough severity rated on a 4-point scale (no cough=1, slight coughing=2,moderate coughing = 3, severe coughing = 4). Coughing is considered slight if no more than 2 coughs in sequence occurred, moderate if 3-5 coughs in sequence occurred and severe if more than 5 coughs in sequence occurred.
3. Hemodynamic variables (blood pressure and heart rate).
4. Modified Ramsay sedation scores during procedure.
5. Patient's comfort and tolerance to fiberscope assessed by Puchner comfort scale[22].
6. Recovery time.
7. Arterial blood gases (PO_2, PCO_2 and PH) before and after the operation.
8. The incidence of postoperative nausea and vomiting .
9. Satisfaction scores of the patient, bronchoscopist and anaesthesiologist.
10. The willingness of the patient to undergo repeat bronchoscopy.
11. Visual analog scale (VAS, 0-100mm) scores of sore throat at 30 min after the end of the operation.
12. Complications related to the procedure and anaesthesia.

Statistical methods

The analysis will be performed on an intention-to-treat basis, such that each patient is analyzed in the group to which he or she is randomized, regardless of actual compliance with the intended intervention. All the analyses will be conducted using Stata 16.0 (STATACORP LLC.4905 Lake Way Drive). A two-tailed p value equal or less than 0.05 will be considered as statistically significant. All tests, except for the primary outcome, will be exploratory. When individual items are missing from a scale, we will calculate the percent of missing items. If less than 10%, we will impute values using the mean of the remaining items. If more than 10%, the scale score will be missing, and unavailable for analysis.

Sample size calculation

Our previous study (unpublished) shows that the incidences of hypoxemia in the two groups are 10% (1/10) in sufentanil group and 27.27% (3/11) in remifentanil group. We determined that enrolment of 270 patients would provide a power of 90% to show a reduction in the rate of incidences of hypoxia between two groups at a two-sided alpha level of 0.05, accounting for 20% lost to follow-up.

Descriptive statistics

Continuous variables will be described using means and SD for normally distributed data. For continuous variables with non-normally distributed data, medians and ranges will be used. Categorical data will be described using counts, proportions, and risk ratios with 95% CIs.

Planned outcome analysis

Primary outcome

The incidences of hypoxia will be compared between the two groups using a $\chi 2$ test or an exact Fisher's exact test if required. The incidences of hypoxia will then be modelled (secondary analysis) using a multivariate logistic regression.

Secondary outcomes

Secondary endpoints will be compared between the two treatment groups by means of Student's t-test (or the Mann-Whitney U test, if necessary) for continuous quantitative variables and by means of the $\chi 2$ test (or Fisher's exact test) for qualitative variables. Linear models and logistics models will be used to compare the two groups in multivariate analyses. Time-to-event analyses will involve the Kaplan-Meier method and the Cox proportional hazards model.

DISCUSSION

MAC is a specific anaesthesia service performed by a qualified anaesthesia provider for a diagnostic or therapeutic procedure[23]. MAC is useful in patients who require repeated fiberoptic bronchoscopy as well as safe in respiratory depression when

performed by experienced anaesthesiologists [24]. We will utilize MAC for patients with severe tracheal stenosis that requires fiberoptic bronchoscopy in this study.

TCI allows an accurate adaptation of the anaesthesia level and fewer overdose-linked adverse effects. As a decreased cumulative dose of sufentanil or remifentanil, hemodynamic stability, recovery and discharge may also be improved by using TCI. The Ce of sufentanil and remifentanil used in the study are based on our previous unpublished research.

This trial is the first randomized controlled study powered to test the hypothesis that sufentanil TCI compared with remifentanil TCI for MAC can reduce the incidence of hypoxemia and related adverse events in patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy. We believe that the findings of this study will have significant clinical implications. This might mean that more studies are needed to determine the optimal strategies for anaesthesia management to prevent hypoxemia.

Ethics and dissemination

Ethics approval and consent to participate

This clinical study will be conducted following the Declaration of Helsinki. It will be conducted in compliance with the protocol, good clinical practice (GCP), designated standard operating procedures, and local laws and regulations relevant to the country of conduct. The study protocol was approved by the Ethics Committee of Shanghai Pulmonary Hospital of China (approval No. K19-122). Informed consent must be obtained from all patients.

Dissemination policy

The results of this study will be disseminated regardless of the effect of the intervention on study outcomes. The manuscript describing the effect of the intervention will be submitted to a peer-reviewed journal when data collection and analyses are complete.

Data collection, monitoring and management

Preoperative, intraoperative and postoperative follow-up data will be collected from electronic medical records, monitoring machines and relevant manual records by the research staff (YJZ). All electronic and handwriting data will be stored on a password-protected computer. Data will be recorded on a standardised paper form (Supplementary file 3) and subsequently double-entered using Epidata software v3.1 by two trained research assistants. Data and safety monitoring will be the responsibility of the principle investigator (JML).

Trial status

The recruitment commenced in February 2021. It is anticipated that recruitment will end by June 2023. The version number of the protocol are v3.0.

Patient and public involvement

Patients or the public were not involved in the design of our research and will not be involved in conduct, reporting or dissemination of our research.

Contributors

WW and YZ designed the study, they are joint first author. WW and YJZ wrote the manuscript together. YZ provided substantial contributions to the conception and design of the study, wrote the statistical analysis plan and estimated the sample size. JML was responsible for designing the study and drafting the work, revising it critically for important intellectual content and approved the final version of the manuscript. All authors gave their agreement to be accountable for all aspects of the work, and ensure the accuracy and integrity of any part of the work.

Funding

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Patient consent for publication

Not required.

Competing interests

The authors declare that they have no competing interests.

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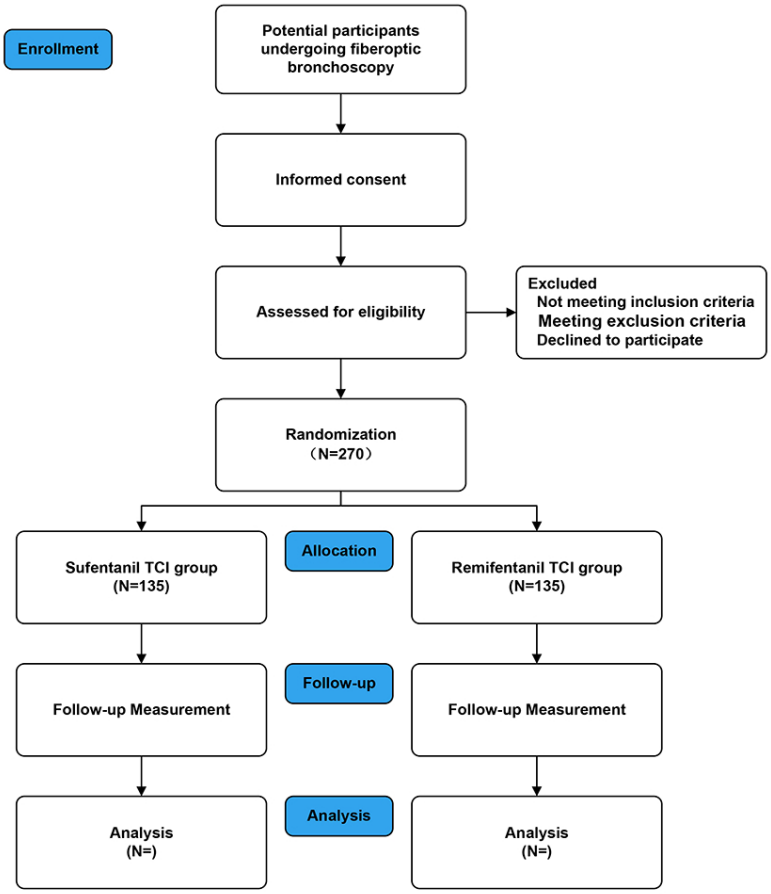
Figure 1
CONSORT flow diagram for the study. CONSORT, Consolidated Standards of Reporting Trials.

Figure 2
SPIRIT Figure-Schedule of enrolment, interventions, and assessments. SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.



CONSORT flow diagram for the study. CONSORT, Consolidated Standards of Reporting Trials.

STUDY PERIOD					
	Enrolment	Allocation	Post-allocation		Close-out
TIMEPOINT	t_{-1}	t_0	t_1	t_2	t_3
	Feb 2021-Jun 2023		During the procedure	PACU	
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Sufentanil TCI			X		
Remifentanil TCI			X		
ASSESSMENTS:					
Baseline variables	X	X			
Hypoxemia			X		
Cough severity			X		
Hemodynamic variables			X		
Sedation scores			X		
Patient's comfort			X		
Recovery time				X	
Postoperative nausea and vomiting				X	
Satisfaction				X	
Visual analog scale				X	

SPIRIT Figure-Schedule of enrolment, interventions, and assessments. SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	YES
Protocol version	3	Date and version identifier	11
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,12
	5b	Name and contact information for the trial sponsor	1,12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2-4
	6b	Explanation for choice of comparators	2-4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5-6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variables (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6-7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10-11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	8-9
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9-10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10-11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10-11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2,12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	10-11

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11-12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	11-12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11-12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11-12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11-12
	31b	Authorship eligibility guidelines and any intended use of professional writers	11-12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11-12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Translated ICFs can be provided on request
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Practice name:
Participant ID:

Informed Consent

Informed Consent form for patient.

This Informed Consent Form is for men and women who attend Shanghai Pulmonary Hospital and who we are inviting to participate in research on anesthesia for bronchoscopy.

The title of our research project is: *Sufentanil target controlled infusion (TCI) vs remifentanil TCI for monitored anaesthesia care for patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy*.

Principal Investigator: Jianming Liu, MD
Organization: Department of Anaesthesiology, Shanghai Pulmonary Hospital, Tongji University School of Medicine

This Informed Consent Form has two parts:

1. Information Sheet (to share information about the research with you)
2. Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the full Informed Consent Form

PART 1: Information Sheet

Introduction

I am Jianming Liu, working for department of Anaesthesiology. We are doing research on monitored anaesthesia care for patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy. I am going to give you information and invite you to be part of this research.

You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research. There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.)

Purpose of the research

Bronchoscopy has been an integral part of the diagnosis and treatment of patients with tracheal stenosis. The two opioids most commonly used are sufentanil and remifentanil. We aim to conduct a trial comparing sufentanil with remifentanil in patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy.

Participant selection

We are inviting all adults with severe tracheal stenosis attend Shanghai Pulmonary Hospital to participate in the research.

Voluntary Participation

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will offer the treatment that is routinely offered, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.

Procedures and Protocol

Participants will be randomly assigned to one of two groups. Participants in one group will be given monitored anesthesia care (MAC) using sufentanil target controlled infusion. Participants in the other group will be given monitored anesthesia care (MAC) using remifentanil. We will then compare which of the two has the best results. The healthcare workers will be looking after you and the other participants very carefully during the study. If we are concerned about what the treatment is doing, we will find out which treatment you

are getting and make changes. If there is anything you are concerned about or that is bothering you about the research please talk to me or one of the other researchers.

For any clinical study (if relevant):

We will take arterial blood from your arm using a syringe through arterial line. This blood taken is painless. In total, we will take about 2 samples of 1 ml arterial blood. At

the end of the research any left-over blood sample will be destroyed).

Description of the Process

In the first time, a small amount of blood, equal to about a teaspoon, will be taken from your arm with a syringe through arterial catheter. This blood will be tested with a blood analyzer. We will ask you a few questions about your general health.

You'll be anesthetized during fiberoptic bronchoscopy. After treatment we'll draw your blood and also ask you a few questions.

Duration

The research takes place over 1/2 days.

Risks

Any risk can appear during the process. Mechanical complications of fiberoptic bronchoscopy include nasopharyngeal, vocal cord, and airway trauma as well as bronchospasm, laryngospasm, pulmonary derecruitment/atelectasis, pneumothorax, airway hemorrhage, and introduction or exacerbation of infection. Systemic complications are primarily related to the procedure itself, medication administration, or patient comorbidities. The healthcare workers will be looking after you and the other participants very carefully during the study. If we are concerned about what the treatment is doing, we will find out which treatment you are getting and make changes.

Benefits

If you participate in this research, you will have the following benefits: any interim illnesses will be treated at no charge to you. The Fresenius DPS workstation for TCI used for free. Your participation is likely to help us find the answer to the research question.

Reimbursements

Your participation is free. You will not be given any other money or gifts to take part in this research.

Confidentiality

With this research, something out of the ordinary is being done in your community. It is possible that if others in the community are aware that you are participating, they may ask you questions. We will not be sharing the identity of those participating in the research.

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except [Yi Zhou and Jianming Liu) who will have access to the information.

Sharing the Results

The knowledge that we get from doing this research will be shared with you through community meetings before it is made widely available to the public. Confidential information will not be shared. After these meetings, we will publish the results in order that other interested people may learn from our research.

Right to Refuse or Withdraw

You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.

Alternatives to Participating

If you do not wish to take part in the research, you will be provided with the established standard treatment available at our hospital.

Who to Contact

If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following:
DR. Jianming Liu, Phone: 86-18019285297
This proposal has been reviewed and approved by the Ethics Committee of Shanghai Pulmonary Hospital of China (approval No. K19-122) which is a committee whose task it is to make sure that research participants are protected from harm.

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

PART 2: Certificate of Consent

This section should be written in the first person and have a statement similar to the one in bold below. If the participant is illiterate but gives oral consent, a witness or a legally authorized representative must sign. A researcher or the person going over the informed consent must sign each consent. The understanding should perhaps be better tested through targeted questions during the reading of the information sheet (some examples of questions are given above), or through the questions being asked at the end of the reading of the information sheet, if the potential participant is reading the information sheet him/herself.

		Please initial each box
1	I have read the foregoing information, or it has been read to me.	☐
2	I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction.	☐
3	I consent voluntarily to participate as a participant in this research.	☐

Print Name of Participant _____

Signature of Participant _____

Date(Day/month/year) _____

If illiterate

Aliterate witness or legally authorized representative must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.

		Please initial each box
1	I have witnessed the accurate reading of the consent form to the potential participant	☐
2	I have witnessed the individual has had the opportunity to ask questions.	☐
3	I confirm that the individual has given consent freely.	☐

Print Name of witness or legally authorized representative _____

Signature of witness or legally authorized representative _____

Date(Day/month/year) _____

Thumb print of participant ☐

Statement by the researcher/person taking consent

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands.

I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher _____

Signature of Researcher _____

Date(Day/month/year) _____

Protocol No:	P20200828V3		
Site	☐☐	**Subject ID:**	☐☐☐
Randomisation No:	☐☐	**Subject Initials:**	☐☐☐☐
Investigator Identifier:	☐☐☐		

Case Report Form

Sufentanil target controlled infusion (TCI) vs remifentanil TCI for monitored anaesthesia care for patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy

By

Shanghai Pulmonary Hospital

Inclusion Criteria

Subjects who meet the following criteria may be included in the study. Did the subject meet the following criteria requirements for inclusion? (√ Yes or No)		Yes 1	No* 2
01	Cotton-Myer grades II-III		
02	Aged 18–65 years		
03	ASA I-III		

* If No, document on Subject Eligibility Page.

Exclusion Criteria

The following will exclude potential subjects from the study. Does the subject have any of the following? (√ Yes or No)		Yes* 1	No 2
01	BMI>30 or < 18.5		
02	Baseline oxygen desaturation (resting SpO_2 <90%)		
03	Pregnancy		
04	History of allergy to related drugs		
05	Severe coagulation dysfunction		
06	Severe hepatic and renal dysfunction		
07	Gastroesophageal reflux disease		
08	History of abnormal recovery from anaesthesia		
09	No informed consent		

*If Yes, document on Subject Eligibility Page

Information Session

Date of Information Session	Did the subject attend the Information Session?	Comments
_____/_____/_____ DD / MM / YY	1 ☐Yes 2 ☐No（explain, if No）	

Subject Eligibility

Date the Subject Signed the Informed Consent Form:	_____/_____/_____ DD / MM / YY
Did the subject meet all of the inclusion/exclusion criteria?	1☐Yes 2☐No

If the subject did not meet all of the Inclusion/Exclusion criteria, provide criterion number and explanation below.

Category	Inclusion/ Exclusion No.	Explanation	Exemption Granted?	If Yes, Date Granted DD/MM/YYYY
1☐Inclusion 2☐Exclusion			1☐Yes 2☐No	___/___/___
1☐Inclusion 2☐Exclusion			1☐Yes 2☐No	___/___/___
1☐Inclusion 2☐Exclusion			1☐Yes 2☐No	___/___/___

Demographics

Date DD/MM/YYYY	Date of Birth DD/MM/YYYY	Gender	Ethnicity
☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	1☐Male	1☐Han
		2☐Female	2☐Non-han
Body Measurements			
Were Body Measurements Collected?		Date DD/MM/YYYY	
1☐Yes 2☐No		☐☐/☐☐/☐☐☐☐	
Parameter	Unit	Result	
Height	cm	☐☐☐	
Weight	Kg	☐☐☐	
Vital Signs			
Were Body Measurements Collected?		Date	
1☐Yes 2☐No		☐☐/☐☐/☐☐☐☐	
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Body Temperature	°C	☐☐.☐	
12-Lead Electrocardiogram Report			
Was ECG performed?		Date DD/MM/YYYY	Actual Time 24-hour clock
1☐Yes 2☐No		☐☐/☐☐/☐☐☐☐	☐☐:☐☐
ECG Interpretation:	1☐Normal	2☐Abnormal, NCS	3☐Abnormal
Comments Regarding CS Findings:			

Medical History

Does the subject have any relevant medical history?		Date DD/MM/YYYY	
1☐Yes 2☐No		____/____/_____	
Diagnosis/Procedure	Date of Onset DD/MM/YYYY	Date of Resolution DD/MM/YYYY	
1	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
2	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
3	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
4	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
5	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
6	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
7	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
8	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING
9	☐☐/☐☐/☐☐☐☐	☐☐/☐☐/☐☐☐☐	9☐ONGOING

Laboratory Analysis

Parameter	Unit	Result
SPO_2		☐☐☐
Arterial blood gas analysis		
PH		☐.☐☐
$PaCO_2$	mmHg	☐☐☐
PaO_2	mmHg	☐☐☐
HCO_3	mEq/L	☐☐

Intervention Phase

Date DD/MM/YYYY	____/____/____			
Group	1☐Group R		2☐Group S	
Whether or not hypoxemia occurs				
1☐subclinical hypoxemia (SPO2 of 90-95%),	2☐moderate hypoxemia (SPO2 of 75-89%, ≤60 s		3☐severe hypoxemia (SpO2 < 90% for >60 s or SpO2 < 75% at any time)	
Management of hypoxemia				
1☐patient stimulation	2☐increasing the volume of supplementary oxygen	3☐jaw-thrust maneuver	4☐mask ventilation	5☐ mechanical ventilation.
Puchner five-point fiber-optic intubation comfort scale				
1☐No reaction	2☐Slight grimacing	3☐Heavy grimacing	4☐Verbal objection	5☐Defensive movement

T0	10 minutes after entering the operation room	
Parameter	Unit	Result
Systolic Blood Pressure	mmHg	☐☐☐
Diastolic Blood Pressure	mmHg	☐☐☐
Heart Rate	beats/minute	☐☐☐
Respiratory Rate	breaths/minute	☐☐
Spo2		☐☐☐

T1	Cp and Ce has achieved equilibrium		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐

	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T2	When bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T3	1 minute after bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T4	5 minutes after bronchoscope is inserted	
Parameter	Unit	Result
Systolic Blood Pressure	mmHg	☐☐☐

Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T5	10 minutes after bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T6	15 minutes after bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐

	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T6	20 minutes after bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T7	25 minutes after bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T8	30 minutes after bronchoscope is inserted	
Parameter	Unit	Result
Systolic Blood Pressure	mmHg	☐☐☐

Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

T9	60 minutes after bronchoscope is inserted		
Parameter	Unit	Result	
Systolic Blood Pressure	mmHg	☐☐☐	
Diastolic Blood Pressure	mmHg	☐☐☐	
Heart Rate	beats/minute	☐☐☐	
Respiratory Rate	breaths/minute	☐☐	
Spo2		☐☐☐	
Ramsay Sedation Scale	1☐	2☐	3☐
	4☐	5☐	6☐
	7☐	8☐	
Cough	1☐	2☐	3☐
	4☐	5☐	6☐
EtCO2	mmHg	☐☐	

Type of fiberoptic bronchoscopy procedure				
1☐Diagnostic		2☐Therapeutic		
If it is Therapeutic bronchoscopy				
1☐Injection of medication	2☐Endotherm knife	3☐Cryotherapy		
4☐Laser	5☐Stent			
Operation time	☐☐☐☐	min	Endoscopist	☐☐☐
Satisfaction scores of bronchoscopist	1☐	2☐	3☐	
	4☐	5☐		
Satisfaction scores of anaesthesiologist	1☐	2☐	3☐	
	4☐	5☐		

Vasoactive drugs used				
Whether or not vasoactive drugs are used	1☐Yes	2☐No		
Vasoactive drug type		name	dosage	whether it is effective or not
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents			1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents			1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents			1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents			1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents			1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents			1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No
1☐vasoconstrictor 2☐vasodilator 3☐Inotropic agents			1☐☐☐☐ μg 2☐☐☐☐ mg	1☐Yes 2☐No

Post Intervention Phase

Recovery time	☐☐☐	min		
Whether nausea and vomiting occur				
1☐Yes	2☐No			
Assessment of PONV				
1☐Mild	2☐moderate	3☐severe		
Satisfaction scores of the patient				
1☐	2☐	3☐	4☐	5☐
willingness of the patient to undergo repeat bronchoscopy.				
1☐Not at all likely	2☐1–3	3☐4–6	4☐7–9	5☐ Extremely likely (10)
VAS scores of sore throat				
1☐	2☐	3☐	4☐	5☐
6☐	7☐	8☐	9☐	10☐
T10	At PACU			
Parameter	Unit	Result		
Systolic Blood Pressure	mmHg	☐☐☐		
Diastolic Blood Pressure	mmHg	☐☐☐		
Heart Rate	beats/minute	☐☐☐		
Respiratory Rate	breaths/minute	☐☐		
Spo2		☐☐☐		
Ramsay Sedation Scale	1☐	2☐	3☐	
	4☐	5☐	6☐	
	7☐	8☐		
Cough	1☐	2☐	3☐	4☐
Arterial blood gas analysis				
PH		☐.☐☐		
$PaCO_2$	mmHg	☐☐☐		
PaO_2	mmHg	☐☐☐		
HCO_3	mEq/L	☐☐		

Adverse Event information

Whether adverse events occurred		
1□Yes	2□No	
Whether serious adverse events occurred		
1□Yes	2□No	
Describe the AE and the connection to project procedures		
AE onset date	□□/□□/□□□□	DD/MM/YYYY
AE stop date	□□/□□/□□□□	DD/MM/YYYY
Date of AE awareness	□□/□□/□□□□	DD/MM/YYYY
Severity		
1□mild	2□moderate	3□severe
Outcome		
1□recovered/resolved	2□recovered/resolved with sequelae	3□study participant died
4□continuing	5□unknown	6□other
SAE causality		
1□Not related	2□Unlikely	3□Possibly
4□Probably	5□Definitely	
Describe the AE and the connection to project procedures		
AE onset date	□□/□□/□□□□	DD/MM/YYYY
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Date of AE awareness	□□/□□/□□□□	DD/MM/YYYY
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