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

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ABSTRACT

Introduction The use of monitored anaesthesia care (MAC) is necessary and ubiquitous for fiberoptic bronchoscopy. Anaesthetic 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, randomised 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 hypoxaemia (an oxygen saturation of <90%). The secondary outcome investigates the severity of hypoxaemia, cough severity, haemodynamic 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.

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 USA annually. Sedation is now generally recommended for all patients undergoing fiberoptic bronchoscopy unless a specific contraindication to sedation exists. Sedation during fiberoptic bronchoscopy improves patient comfort and tolerance and enhances the willingness to repeat the procedure, without increasing complications.

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

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 makes it suitable for anaesthesia management of diagnostic procedures.
and therapeutic bronchoscopy.\textsuperscript{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 haemodynamic instability when effectively inhibiting operational stress, which is often very dangerous for patients with severe tracheal stenosis.\textsuperscript{14} Remifentanil is a more potent opioid than remifentanil, its analgesic effect lasts longer and it is superior in terms of haemodynamic stability. Sufentanil has a longer half-time as compared with remifentanil, but target controlled infusion (TCI) will prevent long-acting opioid-induced accumulation and allow rapid recovery from anaesthesia.\textsuperscript{16} There have been no detailed investigations on the efficacy and safety of monitored anaesthesia 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 randomised controlled trial comparing sufentanil TCI with remifentanil TCI and assume that sufentanil TCI would decrease the incidence of hypoxaemia.

Primary objective

Determine the incidence of hypoxaemia 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-centre, randomised, investigator-initiated clinical trial of 270 patients with severe tracheal stenosis that requires fiberoptic bronchoscopy. The Consolidated Standards of Reporting Trials flow chart is presented in figure 1. A Standard Protocol Items: Recommendations for Interventional Trials figure is included in figure 2 with a checklist included as an additional document (online supplemental 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 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 box 1.

Recruitment

Consecutive patients who present to respiratory clinics at Shanghai Pulmonary Hospital with a diagnosis of tracheal stenosis requiring fiberoptic bronchoscopy will be invited to participate. The flow chart is presented in figure 1. A SPIRIT figure is included in figure 2 with a checklist included as an additional document (online supplemental 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.

Figure 1 CONSORT flow diagram for the study. CONSORT, Consolidated Standards of Reporting Trials; TCI, target controlled infusion.

Figure 2 SPIRIT figure-schedule of enrolment, interventions and assessments. PACU, postanaesthesia care unit; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; TCI, target controlled infusion.
Box 1 Summary of exclusion criteria of the trial

Exclusion criteria
1. Body mass index >30 or <18.5 kg/m²
2. Baseline oxygen desaturation (resting SpO₂<90%).
3. Chronic opioid treatment, substance abuse or drug use.
4. Pregnancy.
5. History of allergy to related drugs.
6. Severe coagulation dysfunction.
7. Severe hepatic and renal dysfunction.
8. Gastro-oesophageal reflux disease.
9. History of abnormal recovery from anaesthesia.
10. No informed consent.
11. Patients with acute exacerbation of chronic obstructive pulmonary disease.

stenoisis and meet the inclusion criteria will be offered the opportunity to enrol 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 authorised representative (LAR) prior to enrolment 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 online supplemental file 2.

Randomisation 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. Randomisation 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 V.16.0 (StataCorp). Randomisation envelopes to be opened will be created by the research assistant (RA) just prior to when they are ready to randomise a patient. The integrity and presence of the envelopes will be checked at each monitoring visit.

The RA who will be blinded to the randomised assignment of patients will conduct all baseline interviews. The patients will be blinded to their intervention as will the research staff completing the postprocedural 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 intravenous 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 postanaesthesia care unit discharge). All patients will receive oxygen application via a nasal tube with 2 L of O₂/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 O₂/min and an adjustable pressure-limiting valve setting of 30 cmH₂O. Both groups will be intravenously administered an initial loading dose of 0.8mcg/kg dexmedetomidine, followed by a maintenance dose of 0.5 mcg/(kg·h) during the procedure. A 4mL of 1% lignocaine solution will be administered by nasopharyngeal airway to throat, then three aliquots of 4mL 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.35 A BF-260 electronic bronchoscope (BF-1T260/6C260, Olympus, Japan) will be used. The airway will be fully assessed and the appropriate interventional procedure will be performed to relieve the obstruction and stabilise 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, various 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 10–20mg 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 60mm Hg is regarded as hypotension. In the event hypotension happens, an intravenous injection of phenylephrine (25–100µg) will be administered as a rescue vasopressor.

Management of hypoxaemia
Definition of hypoxaemia: SpO₂<90% at any time.20 The severity of hypoxaemia is classified as follows: subclinical hypoxaemia (SpO₂ of 90%–95%), moderate hypoxaemia (SpO₂ of 75%–89%, ≤60s) and severe hypoxaemia (SpO₂<90% for >60s or SpO₂<75% at any time).21

Once hypoxaemia develops, it will be corrected using the following sequence: (1) patient stimulation, (2) increasing the volume of supplementary oxygen from 6 to 10 L of O₂/min, (3) opening the airway using a jaw-thrust manoeuvre, (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 hypoxaemia.

**Secondary outcomes**
Secondary outcome variables include the following:

1. The severity of hypoxaemia.
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 two coughs in sequence occurred, moderate if 3–5 coughs in sequence occurred and severe if more than five coughs in sequence occurred.
3. Haemodynamic 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 Analogue Scale (0–100 mm) 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 analysed in the group to which he or she is randomised, regardless of actual compliance with the intended intervention. All the analyses will be conducted using Stata V.16.0 (StataCorp). 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 hypoxaemia 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 hypoxaemia 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 in respiratory depression when performed by experienced anaesthesiologists.24 We will use 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, haemodynamic 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 randomised controlled study powered to test the hypothesis that sufentanil TCI compared with remifentanil TCI for MAC can reduce the incidence of hypoxaemia 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 hypoxaemia.

**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, 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 (YuZ). All electronic and handwriting data will be stored on a password-protected computer. Data will be recorded on a standardised paper form (online supplemental file 3) and subsequently double-entered using Epidata software V.3.1 by two trained RAs. Data and safety monitoring will be the responsibility of the principle investigator (JL).

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 V.3.0.

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.

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Contributors
WW and YZ designed the study, they are joint first author. WW and YuZ wrote the manuscript together. YIZ provided substantial contributions to the conception and design of the study, wrote the statistical analysis plan and estimated the sample size. JL was responsible for designing the study and drafting 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.

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Competing interests
None declared.

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Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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Supplemental material
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REFERENCES
1 Ernst A, Silvestri GA, Johnstone D, et al. Interventional pulmonary procedures: guidelines from the American College of chest Physicians. Ann Thorac Surg 2012;108:503–11.
2 José RJ, Sjaefl S, Navani N. Anesthesia for bronchoscopy. Curr Opin Anaesthesiol 2014;27:453–7.
3 McCambridge AJ, Boesch RP, Mullon J. Sedation in bronchoscopy: a review. Clin Chest Med 2018;39:65–77.
4 British Thoracic Society Bronchoscopy Guidelines Committee, a Subcommittee of Standards of Care Committee of British Thoracic Society. British thoracic society guidelines on diagnostic flexible bronchoscopy. Thorax 2001;56 Suppl 1:1–21.
5 Maguire GP, Rubinfeld AR, Trembath PW, et al. Patients prefer sedation for fiberoptic bronchoscopy. Respir Med 1998;93:81–5.
6 Putinati S, Ballerin L, Corbetta L, et al. Patient satisfaction with conscious sedation for bronchoscopy. Chest 1999;115:1347–40.
7 Emam W, Mostafa Y, Madkour A, et al. Bronchoscopic management as an alternative treatment in non-operative benign tracheal stenosis. Int J Clin Pract 2005;59:410–5.
8 McGrath EE, Warriner D, Anderson P. The insertion of self expanding metal stents with flexible bronchoscope under sedation for malignant tracheobronchial stenosis: a single-center retrospective analysis. Arch Bronconeumol 2012;48:43–8.
9 Medford ARL, Bennett JA, Free CM, et al. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA): applications in chest disease. Respir Med 2010;105:71–9.
10 Scott LJ, Perry CM, Remifentanil. Drugs 2005;65:1793–823.
11 Berkenbosch J, Graft GR, Stark JM, et al. Use of a remifentanil-propofol mixture for pediatric flexible fiberoptic bronchoscopy sedation. Paediatr Anaesth 2004;14:941–6.
12 Natalini G, Fassini P, Seramondi V. Remifentanil vs. fentanyl during interventional rigid bronchoscopy under general anaesthesia and spontaneous assisted ventilation. European Journal of Anaesthesiology EJA 1999;16.
13 Lee H, Choe YH, Park S. Analgesication during flexible fiberoptic bronchoscopy: comparing the clinical effectiveness and safety of remifentanil versus midazolam/propofol. BMC Pulm Med 2019;19:240.
14 Ryu JH, Lee SW, Lee JH, et al. Randomized double-blind study of remifentanil and dexmedetomidine for flexible bronchoscopy. Br J Anaesth 2012;108:503–11.
15 Rezaiguia-Delcaux S, Lavoiture F, Korchinsky T, et al. Fiber optic bronchoscopy and remifentanil target-controlled infusion in critically ill patients with acute hypoxaemic respiratory failure: a descriptive study. Anaesth Crit Care Pain Med 2017;36:273–7.
16 Caron M, Parrot A, Elhabbi A, et al. Pain and dyspnea control during awake fiberoptic bronchoscopy in critically ill patients: safety and efficacy of remifentanil target-controlled infusion. Ann Intensive Care 2021;11:1–9.
17 Zha B, Wu Z, Xie P, et al. Supraglottic jet oxygenation and ventilation reduces desaturation during bronchoscopy under moderate to deep sedation with propofol and remifentanil: a randomised controlled clinical trial. Eur J Anaesthesiol 2021;38:294–301.
18 Derrode N, Lebrun F, Levron J-C, et al. Influence of peroperative opioid on postoperative pain after major abdominal surgery: sufentanil TCI versus remifentanil TCI. A randomized, controlled study. Br J Anaesth 2003;91:842–9.
19 Kaur H, Dhooria S, Aggarwal AN, et al. A Randomized Trial of 1% vs 2% Lignocaine by the Spray-as-You-Go Technique for Topical Anaesthesia During Flexible Bronchoscopy. Chest 2015;148:739–45.
20 Ryu JH, Lee SW, Lee JH, et al. Randomized double-blind study of remifentanil and dexmedetomidine for flexible bronchoscopy. Br J Anaesth 2012;108:503–11.

Wu W, et al. BMJ Open 2022;12:e058662. doi:10.1136/bmjopen-2021-058662
21 Qin Y, Li LZ, Zhang XQ, et al. Supraglottic jet oxygenation and ventilation enhances oxygenation during upper gastrointestinal endoscopy in patients sedated with propofol: a randomized multicentre clinical trial. Br J Anaesth 2017;119:158–66.

22 Puchner W, Egger P, Pühringer F, et al. Evaluation of remifentanil as single drug for awake fiberoptic intubation. Acta Anaesthesiol Scand 2002;46:350–4.

23 ASA. Position on monitored anesthesia care 2018.

24 Hong KS, Choi EY, Park D-A, et al. Safety and efficacy of the moderate sedation during flexible bronchoscopic procedure: a systematic review and meta-analysis of randomized controlled trials. Medicine 2015;94:e1459–e59.