PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	wu, wei; Zhou, Yi; Zhu, Yuanjie; Liu, Jianming

VERSION 1 – REVIEW

REVIEWER	N. Shallik Hamad Medical Corporation, Doha, Qatar, Anesthesia, ICU and Perioperative Medicine
REVIEW RETURNED	24-Dec-2021

GENERAL COMMENTS	• Keywords need improvement or MESH compatible. • Many missed points in the abstract. • Many points are missed in the limitations of the study • The aim of Bronchoscopy procedures should be clear for example dilation or diagnosis or therapeutics • Many other exclusion criteria should be included (for example lung diseases or COPD or…) • Risk of bronchoscopy in this tight tracheal stenosis should be clear and its treatment if happened. • BIS has to be applied to check the depth of sedation in two groups otherwise what is the target sedation or what is the sedation score that will be used? • Data collection sheet is not attached.

REVIEWER	Tobias Müller University Hospital Aachen
REVIEW RETURNED	25-Jan-2022

GENERAL COMMENTS	In this study protocol the authors describe a trial comparing the use of sufentanil vs. remifentanil during flexible bronchoscopy for the diagnostic work-up of patients with severe tracheal stenosis. In general, the manuscript is well written and the topic is of interest, I have only minor comments: - The authors should provide more details about the interventions performed during the procedure (endobronchial ultrasound, biopsy...) - During the procedure sedation is performed using 4 different sedative drugs: midazolam, dexmedetomidine, propofol and either sufentanil or remifentanil suggesting at least a deep level of sedation. The authors should comment why deep sedation is really necessary to perform the procedure. - The loading dose of dexmedetomidine is given over which time span?

	- This is an ongoing study which started recruitment almost a year ago. The authors should comment why publication of the study protocol is seeked now. - Severe tracheal stenosis is not a common condition. Hence, recruitment of a total of 270 patients might be difficult to achieve. The authors should provide data about the number of patients treated for this condition in the study center.

VERSION 1 – AUTHOR RESPONSE

Response to reviewers #1

We feel great thanks for your professional review work on our article. As you are concerned, there are several problems that need to be addressed. According to your nice suggestions, we have made extensive corrections to our previous draft, the detailed corrections are listed below.

Comments 1: *Keywords need improvement or MESH compatible*

Response: We thank the reviewer for pointing this out, we have corrected it to “Adult anaesthesia, Endoscopic surgery, Bronchoscopy, Chronic airways disease, Respiratory tract tumours”.

Comments 2: *Many missed points in the abstract.*

Response: We agree with the reviewer. We have supplemented the background and Methods analysis in the abstract. We also introduced the secondary outcome of this study in the abstract.

We added to page2:

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.

Comments 3: *Many points are missed in the limitations of the study*

Response: We agree with the reviewer. In respond to this comment, we have revised the text as follows and added to page2-3.

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.

Comments 4: *The aim of Bronchoscopy procedures should be clear for example dilation or diagnosis or therapeutics*

Response: We agree with the reviewer. Both diagnostic sampling and therapeutic interventions can be performed during flexible bronchoscopy in our research.

We have added content to the article about bronchoscopy procedures to page8:

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.

Comments 5: *Many other exclusion criteria should be included (for example lung diseases or COPD or…)*

Response: We acknowledge your comments very much, which are valuable in improving the quality of our manuscript. We added to page5. In order to protect patient rights and ensures research accuracy, one exclusion criterion has been added: Patients with acute exacerbation of chronic obstructive pulmonary disease (COPD). We believe that those patients may require ventilator support because of low breathing reserve which make them unsuitable for study. We agree what more exclusion criteria would be useful to internal authenticity of our study.

We also hope to improving the external validity and increase the usefulness of our study for providing evidence to inform multimorbidity management. As multiple chronic conditions including lung disease does affect the results of our study, a post hoc subgroup analysis conduct will be conducted.

Comments 6: *Risk of bronchoscopy in this tight tracheal stenosis should be clear and its treatment if happened.*

Response: We agree with the reviewer. The bronchoscopy and anesthesia management of these patients has always been challenging. They have a higher rate of complications than ordinary patient. For the notification of related complications, we have described them in detail in the informed consent form (Supplementary file2 Patient Informed Consent).

The complications of flexible bronchoscopy in patients with severe tracheal stenosis can be categorized as mechanical or systemic. 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. The most consistently reported mechanical complications are related to airway manipulation/trauma and bleeding. Systemic complications are primarily related to the procedure itself, medication administration, or patient comorbidities. Complications related to the procedure include vasovagal syncope, nausea/vomiting, aspiration, and hypoxemia. And comorbidities including myocardial dysfunction, pulmonary insufficiency, or special cases such as increased ICP can predispose to unique complications.

Bronchoscopically-induced bleeding needs special mention. We have a routine medical procedure bronchoscopically-induced bleeding patient. First, the nonbleeding lung will be protected. The patient will be positioned with the bleeding lung in the decubitus, dependent position (if hemodynamics permit), and if necessary, a double lumen tube will have to be placed in the nonbleeding lung. Other methods of bleeding control include the instillation of cooled saline into the bronchus and then clamping the bronchus with the fiberoptic scope tip. If this does not work then 5 mL of thrombin may be instilled, or, alternately, 2 mL of 1:1,000 epinephrine mixed with normal saline in a 1:10 mixture in order to produce vasoconstriction, thereby reducing bleeding[1].

Comments 7: *BIS has to be applied to check the depth of sedation in two groups otherwise what is the target sedation or what is the sedation score that will be used?*

Response: Thank you for pointing out this problem to us. We agree that BIS would be useful to the assessment of depth of sedation. The assessment of depth of sedation is also an important part of our research. We assess the depth of sedation periodically throughout the procedure by utilizing Modified Ramsay Sedation Scale in the study. Original Ramsay Sedation Scale is a 6-item scale developed to assess ICU sedation[2]. However, 8-item Modified Ramsay Sedation Scale is used in our study[3]. We are really sorry that we didn't make it clear in the original manuscript. We have modified the expression of the scale in the revised manuscript (Page8). As mentioned, EEG monitors, such as the bispectral index monitor is not used in the trial. The main reasons are as follows: First, multiple observational studies find a significant correlation between the processed EEG index and the sedation scale. However, there is a lack of discrimination of index value associated with each sedation state[4-6]. so, a particular index value can herald several different sedation states. Second, the provision of analgesics can further confound the relationship between processed EEG index and sedation depth. Third, several studies have shown that during shorter procedures, such as flexible bronchoscopy and colonoscopy, sedation care guided by processed EEG show no benefit[7]. In addition, the main target of our study is about hypoxemia. We hope, in the future, to apply BIS to evaluate the depth of sedation for patients with severe tracheal stenosis undergoing fiberoptic bronchoscopy.

Comments 8: *Data collection sheet is not attached.*

Response: We sincerely appreciate the valuable comments. The data collection sheet for the study has been added in the attachment (Supplementary file3 Case Report Form). We have added to page11: 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.

Response to reviewers #2

Thank you for the many insightful comments and suggestions. We have made revisions to address all the comments. A list of our responses to each of the specific comments is listed below.

Comments:

In this study protocol the authors describe a trial comparing the use of sufentanil vs. remifentanil during flexible bronchoscopy for the diagnostic work-up of patients with severe tracheal stenosis. In general, the manuscript is well written and the topic is of interest, I have only minor comments:

We also appreciate your clear and detailed feedback and hope that the explanation has fully addressed all of your concerns. In the remainder of this letter, we discuss each of your comments individually along with our corresponding responses.

Comment 1: *The authors should provide more details about the interventions performed during the procedure (endobronchial ultrasound, biopsy...)*

Response: Thanks for this thoughtful comment. Both diagnostic sampling and therapeutic interventions can be performed during flexible bronchoscopy in our research. We have added content to the article about bronchoscopy procedures to Page8.

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.

Comment 2: *During the procedure sedation is performed using 4 different sedative drugs: midazolam, dexmedetomidine, propofol and either sufentanil or remifentanil suggesting at least a deep level of sedation. The authors should comment why deep sedation is really necessary to perform the procedure.*

Response: We agree with the reviewer. Patients in our study tended to achieve a relatively deep degree of sedation. The main reasons are as follows: First, the degree of noxious stimulation caused by the insertion and manipulation of a bronchoscope (both flexible and rigid) is often similar to a surgical incision[8]. Patients with severe tracheal stenosis, who are more sensitive to airway stimulation, reported poor tolerance for bronchoscope. Second, we hope to reduce cough and prevent cardiovascular instability, such as hypotension, hypertension, bradycardia, and tachycardia, during flexible bronchoscopy. Third, evaluations based on patient satisfaction after bronchoscopy clearly also indicate that utilization of deep sedation services for endoscopic procedures improves acceptability[9]

Comment 3: *The loading dose of dexmedetomidine is given over which time span?*

Response: Thanks for this valuable comment. When patients are transferred to the operating theatre and monitored with ECG, pulse oximetry, and non-invasive arterial pressure, they will receive a loading dose of 0.8mcg/kg dexmedetomidine over 10 min. The TCI of sufentanil or remifentanil will start after the loading dose of dexmedetomidine is given.

Comment 4: *This is an ongoing study which started recruitment almost a year ago. The authors should comment why publication of the study protocol is seeked now.*

Response: We sincerely appreciate the valuable comments. We consider the COVID-19 pandemic to be a “black swan” event, which has broad effects on our research. Shanghai has put all its 26 million residents under lockdown over the year. Patients can't go to hospital but stay at home, therefore we have encountered great difficulties in participant enrollment. We seek to have our study protocol published in order to make the public know about our work and facilitate collaboration with other researchers. We also believe that this manuscript is appropriate for publication because it making it easier for researchers to stay up to date in the fields of anaesthetic management

Comment 5: Severe tracheal stenosis is not a common condition. Hence, recruitment of a total of 270 patients might be difficult to achieve. The authors should provide data about the number of patients treated for this condition in the study center.

Response: We agree with the reviewer. Severe tracheal stenosis is not very common. Iatrogenic trauma is the most common cause of tracheal stenosis in adults. The incidence rate of tracheal stenosis following laryngotracheal intubation and tracheostomy has been said to range from 6% to 21% and 0.6% to 21%, respectively[10-12] .The total bronchoscope volume was 22934 in 2020 and 26331 in 2021 at our respiratory endoscopy center. A total of 358 patients with severe tracheal stenosis were treated in our center in 2021.

VERSION 2 – REVIEW

REVIEWER	Tobias Müller University Hospital Aachen
REVIEW RETURNED	31-May-2022

GENERAL COMMENTS	All points have been sufficiently adressed by the authors.

VERSION 2 – AUTHOR RESPONSE

Response to reviewers #2

We feel great thanks for your professional review work on our merits.

Comments 1: *All points have been sufficiently addressed by the authors.*

Response: We would like to thank you for your careful reading, helpful comments and constructive suggestions which has significantly improve the presentation of our manuscript.