

Inhibition of Stress and Spontaneous Respiration: Efficacy and Safety of Monitored Anaesthesia Care by Remifentanil in Fiberoptic Bronchoscopy for Patients with Severe Tracheal Stenosis

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Research Article

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Abstract

Objective To determine the effective concentration of target-controlled infusion (TCI) of remifentanyl used to inhibit stress during the treatment of severe tracheal stenosis with fibreoptic bronchoscopy and to evaluate the safety of the monitored anaesthesia care (MAC) by remifentanyl.

Methods A study of 60 patients with severe tracheal stenosis who underwent diagnostic and therapeutic fibreoptic bronchoscopy at Shanghai Pulmonary Hospital affiliated with Tongji University was performed. Dexmedetomidine was initially administered at a bolus dose (0.8 mcg/kg), followed by a 0.5 mcg/(kg·h) continuous infusion. Remifentanyl was administered by TCI. When the target concentration was reached, the nasopharyngeal airway was inserted, and then oxygen was supplied by a connected anaesthesia machine. The effective concentration of remifentanyl was titrated by the improved sequential method, and 30 patients were included. The EC95 of remifentanyl was set as the plasma target concentration to evaluate the safety of the MAC, and another 30 patients were included. Remedy measures: Propofol (10-20 mg) was injected intravenously. The primary outcome measures were the cough score and the incidence and severity of hypoxemia. The tolerance score for nasopharyngeal airway placement, Ramsay sedation score, haemodynamic changes, satisfaction score, patients' 24 h recall score, patients' willingness to re-receive the procedure, and related adverse events were recorded.

Results On the basis of sedation with dexmedetomidine, the EC95 of remifentanyl for inhibiting the stress response in fibreoptic bronchoscopy performed on patients with severe tracheal stenosis was 2.710 ng/ml (95% CI, 2.471-4.473 ng/ml), and the EC50 was 2.243 ng/ml (95% CI, 2.061-2.446 ng/ml). Among the 30 patients who received an EC95 of remifentanyl as the target concentration, 1 patient was remedied by injecting propofol; the tolerance score for insertion of the nasopharyngeal airway was 2, the score of Ramsay sedation was 3, and the cough score was 1. The incidence of respiratory depression was 50%, the incidence of hypoxemia was 20%, and 86.7% of patients with respiratory depression returned to normal by awakening. One patient returned to normal by mask-assisted ventilation, and another returned to normal by laryngeal mask mechanical ventilation. The satisfaction score of the operator was 9, the satisfaction score of the anaesthesiologist was 8, the satisfaction score of the patients was 10, the score of the patients' 24 h operative recall was 1, the rate of patient willingness to re-accept the procedure was 93.3%, the incidence of throat pain at 30 min after the end of the operation was 16.7%, and the circulation was stable during the operation. No pruritus, nausea, vomiting or other related adverse reactions were reported.

Conclusion MAC using TCI of remifentanyl can effectively inhibit the stress response to fibreoptic bronchoscopy in patients with severe tracheal stenosis while maintaining spontaneous breathing. The patients are safe and comfortable and express high satisfaction, making this method worthy of clinical application.

Trial registration Registration date : 12/02/2021, Registration number: ChiCTR2100043380.

Background

With the development of endoscopic technology, interventional treatment via fiberoptic bronchoscopy has become one of the main methods of diagnosis and treatment for patients with benign and malignant tracheal stenosis, and the demand for fiberoptic bronchoscopic interventional treatment for patients with severe tracheal stenosis continues to increase [1–3]. Compared with ordinary patients, severe patients tend to be anxious and exhibit obvious difficulty breathing, tachycardia, hypersecretion or expectoration of sputum, and lung infections, and they must often be placed in unnatural postures to maintain airway patency. Even if apnoea occurs, most conscious patients cannot tolerate the diagnosis and treatment of fiberoptic bronchoscopy, which could improve airway obstruction [4].

Effective and safe anaesthesia management technology can inhibit the stress response to fiberoptic bronchoscopy in severe patients, reduce the occurrence of choking cough and laryngeal spasm, and reduce serious complications that may be life-threatening, such as asphyxia, massive bleeding and malignant arrhythmia [5, 6]. MAC with spontaneous respiration has significant advantages over local anaesthesia and laryngeal mask general anaesthesia [7–11]. However, there are few studies on anaesthesia management techniques for such severe patients, there is no precise standard scheme, and there is a lack of evidence-based medicine at home and abroad. In our study, on the basis of sedation with dexmedetomidine, the effective concentration of remifentanyl for inhibiting the stress response was titrated through a modified sequential method during fiberoptic bronchoscopy of patients with severe tracheal stenosis, and the safety of the MAC regimen with remifentanyl was evaluated.

Methods

Study design and population

This prospective interventional study was conducted at the respiratory endoscopy centre of Shanghai Pulmonary Hospital affiliated with Tongji University from February 2021 to May 2021. The study was approved by the Ethics Committee of Shanghai Pulmonary Hospital, Tongji University, China (K19-122) and registered in the Chinese Trial Registry (12/02/2021, ChiCTR2100043380). All patients enrolled in this study received informed consent.

Sixty patients who received fiberoptic bronchoscopy treatment were included, all of whom were diagnosed with severe tracheal stenosis for the first time. The effective concentration of remifentanyl was titrated by the improved sequential method in 30 patients, the safety of the MAC protocol was evaluated using EC95 as the plasma target concentration in 30 patients, and the inclusion of patients was completed by LJM. The inclusion criteria included patients with severe tracheal stenosis (the reduced area of the tracheal cavity was more than 50%) who wanted to be treated by fiberoptic bronchoscopy, were aged 18 ~ 65 years, and had ASA I - III status. The exclusion criteria were as follows: abnormal nasal anatomy, severe coagulation dysfunction, severe hepatic and renal dysfunction, history of abnormal recovery from surgical anaesthesia, chronic opioid treatment, substance abuse or drug use, pregnancy,

history of allergy to related drugs, and no informed consent. Included patients were later excluded if general anaesthesia by laryngeal-mask or endotracheal intubation was required for the operation or the operation was over 60 min in duration.

MAC protocol

All patients fasted for 8 h, and water was forbidden for 4 h preoperatively. In the anaesthesia preparation area, 0.03 mg/kg midazolam (Midazolam®, Nihwa, China) was given intravenously to relieve preprocedural anxiety. ECG, HR, SpO₂ and MAP and Rf were monitored regularly after patient entry into the operating room. Oxygen inhalation through a nasal catheter (2 L/min) was performed. A simple mask breathing apparatus and anaesthesia machine were used as a standby. Dexmedetomidine (0.8 mcg/kg, Dexmedetomidine®, Yangtze River, China) was administered within 10 min using a Fresenius DPS workstation, and plasma target-controlled infusion (TCI) of remifentanil (Remifentanil®, Yichang Humanwell, China) was completed within 5 min. When the effector chamber concentration reached the target concentration, a nasopharyngeal airway (No. 6/7, Medis, UK) was placed, and oxygen was given by an anaesthesia machine (6 L/min) with an adjustable pressure-limiting (APL) valve setting of 30 cmH₂O. Four millilitres of 1% lidocaine (Lidocaine®, CSPC, China) was injected through the nasopharyngeal airway for topical anaesthesia, and then fiberoptic bronchoscopy was started. When the fiberoptic bronchoscope (BF-1T260/6C260, Olympus, Japan) was placed, 4 ml of 1% lidocaine was injected through the bronchoscopic tube into the acoustic gateway and subglottis for topical anaesthesia. Intraoperative dexmedetomidine was pumped continuously at 0.5 mcg/(kg·h). The effective concentration of remifentanil was titrated by a modified sequential method. The plasma target concentration of remifentanil in the first patient was 2.5 ng/ml, and the difference between adjacent targets was 0.5 ng/ml. After 3 cycles of negative and positive reactions, the difference in adjacent target concentrations was changed to 0.2 ng/ml. The stress response was defined as positive if the change in HR or MAP exceeded 15% of the baseline or a choking cough affected the operation. Intravenous injection of 10–20 mg propofol was used as a remedy and was used repeatedly if necessary. After obtaining the EC95 of remifentanil, the plasma target concentration was set to EC95 to evaluate the perioperative safety of the MAC during the operation.

Related events and their management: ☒ definition of hypoxemia: SpO₂ < 90% at any time. The severity of hypoxemia was classified as follows: subclinical hypoxemia (SPO₂ of 90–95%), moderate hypoxemia (SPO₂ of 75–89%, ≤ 60 s), and severe hypoxemia (SpO₂ < 90% for > 60 s or SpO₂ < 75% at any time). The treatment process for hypoxemia was as follows: stimulation and awakening, increasing the oxygen flow (10 L/min), supporting the lower jaw, mask-assisted ventilation, and mechanical ventilation with a laryngeal mask. ☒ hypotension: for MAP < 80% of baseline or 60 mmHg, if necessary, an intravenous injection of norepinephrine (25 ~ 100 µg/time) was used to maintain the blood pressure and was repeated when needed. ☒ bradycardia: HR < 50 bmp, with administration of atropine as appropriate; if arrhythmia occurred, vasoactive drugs were administered by the anaesthesiologist based on his or her clinical judgement.

Outcome measures

The primary outcome measures were the cough score and the incidence and severity of hypoxemia. The secondary outcomes included recovery time; dosage of propofol; Ramsay score; arterial blood gas analysis before and after the operation; haemodynamic changes; the tolerance score for nasopharyngeal airway placement; satisfaction scores of the operator, anaesthesiologist and patient; throat pain and epistaxis at 30 min after the end of the operation; throat pain; patients' scores on operation recall and willingness to receive treatment again at 24 h; and related adverse events such as postoperative pruritus, nausea and vomiting, bleeding, haemoptysis requiring invasive re-treatment, pneumothorax, etc.

Statistical analysis

All statistical analyses were performed using SPSS 26.0. Continuous variables are presented as the mean (standard deviation [SD]) or median (interquartile range, [IQR]). The nonnormally distributed data are presented as the median (interquartile range, [IQR]). Categorical variables are presented as counts (%). Continuous variables were compared using the Mann-Whitney U test or T-test. EC95, EC50, the standard error and the logarithm value of the 95% confidence interval (CI) of remifentanyl were calculated by the formula of the sequential method [12]. The sample size of the effective concentration titrated by the improved sequential method is not clearly defined. A sample size of 20–40 has been used in general studies [12]. In the present study, the sample size of the effective concentration titrated by remifentanyl was 30. The safety of 30 patients was also observed. Two-sided p values < 0.05 were considered significant.

Results

Patients

All 63 patients enrolled in the study; 3 patients were excluded because the operation time was more than 60 min, 60 patients were eligible for the data analysis, and none were discontinued due to safety concerns. The flow chart is shown in Fig. 1. Demographic and operation-related data for all 60 patients are shown in Table 1.

Table 1
Patient characteristics (n = 60)

Item	
Age, mean \pm SD, years	48.6 \pm 12.8
Male, n (%)	17(56.7)
Height,mean \pm SD, m	1.7 \pm 0.1
Weight,mean \pm SD, kg	64.8 \pm 9.3
BMI, mean \pm SD, kg/m ²	23.8 \pm 2.6
ASA 1/2 /3, n (%)	0(0)/42(70.0)/18 (30.0)
Classification of airway stenosis	
2/3/4,n (%)	30(50)/24(40) / 6(10)
Indications for bronchoscopy, n (%)	
Malignant tumor of trachea	30 (50.0)
Benign tumor of trachea	14 (23.3)
Stenosis after tracheotomy	6 (10.0)
Tracheomalacia	4 (6.7)
Other	6 (10.0)
Diagnostic interventions, n (%)	
Tumor removal	16(26.7)
Tumor cauterization and cryopreservation	22 (36.7)
Stent placement	18 (30.0)
Balloon dilatation	4(6.7)
Pre-bronchoscopic respiratory parameters	
SpO ₂ , median [IQR], %	96 [95–97]
RR, mean \pm SD, per min	16 \pm 2
PaO ₂ [IQR],mmHg	82.0 [77.0–86.5]
PaCO ₂ [IQR],mmHg	41.5 [40.3–43.7]
Pre-bronchoscopic hemodynamic parameters	
MAP, median, mmHg	96.5 \pm 6.4

Item	
HR, mean \pm SD, beat per min	89.2 \pm 18.1

Effective concentration of remifentanil

Figure 2 shows that the stress response of 30 patients with severe tracheal stenosis during fiberoptic bronchoscopy treatment was treated with remifentanil at different blood concentrations using the modified sequential method. The half effective effect-chamber concentration of remifentanil (EC50) was 2.243 ng/ml (95% CI, 2.061–2.446 ng/ml), and the EC95 was 2.710 ng/ml (95% CI, 2.471–4.473 ng/ml), as shown in Table 2.

Table 2
Confidence interval of remifentanil effective concentration

Confidence limit	95% Confidence limit		
	Estimate	Lower limit	Upper limit
0.01	1.717	0.858	1.937
0.05	1.857	1.13	2.035
0.1	1.936	1.308	2.092
0.15	1.991	1.441	2.134
0.2	2.036	1.555	2.17
0.25	2.076	1.657	2.205
0.3	2.112	1.752	2.241
0.35	2.146	1.84	2.28
0.4	2.179	1.921	2.325
0.45	2.211	1.996	2.38
0.5	2.243	2.061	2.446
0.55	2.276	2.117	2.528
0.6	2.309	2.166	2.628
0.65	2.345	2.207	2.746
0.7	2.383	2.245	2.885
0.75	2.424	2.281	3.05
0.8	2.471	2.317	3.251
0.85	2.527	2.357	3.508
0.9	2.599	2.404	3.866
0.95	2.71	2.471	4.473
0.99	2.931	2.596	5.895

Information related to surgery, hypoxemia and related adverse reactions

For 30 patients with EC95 TCI of remifentanil, haemodynamics were stable at each time point during the operation, as shown in Table 3. One case with remedy by 30 mg propofol was completed. The tolerance

score for nasopharyngeal airway placement, Ramsay sedation score, cough score and satisfaction score are shown in Table 4. The incidence of respiratory depression was 50%, the incidence of subclinical respiratory depression was 30%, the incidence of moderate hypoxemia was 20%, and the incidence of severe hypoxemia was 0%. Among all patients with respiratory depression, 86.7% were restored to normal by awakening, 1 was restored to normal by mask-assisted ventilation, and another was restored to normal by laryngeal-mask mechanical ventilation (Table 5). The analysis of arterial blood gas before and after the operation is shown in Fig. 3. Other sedation-related adverse reactions are shown in Table 6. There were cases of increased heart rate and blood pressure, none of which exceeded 20% of the baseline value. Adverse reactions related to oxygen delivery, including throat pain 30 min and 24 h after the operation, are shown in Table 7.

Table 3
Hemodynamic changes(HR beats/min,MAP mmHg n = 30)

Item	T ₀	T ₁	T ₂	T ₃	T ₄	T ₅
HR	96.4 ± 18.7	80.8 ± 12.9	91.4 ± 17.3	85.3 ± 12.1	80.4 ± 11.1	78.1 ± 8.9
MAP	101.7 ± 10.0	89.9 ± 9.4	99.8 ± 12.2	93.1 ± 8.1	85.9 ± 6.1	85.4 ± 7.3
T ₀ : before procedure,T ₁ procedure T ₂ 5min after procedure T ₃ 10min after procedure T ₄ 15min after procedure T ₅ end of procedure						

Table 4
 Procedure data, propofol dosage and satisfaction (n = 30)

Characteristic	
Procedure time, min	25.7 ± 8.1
Recovery time, min [IQR]	2 [1.0–2.3]
Sedation score [IQR]	3 [3–4]
Nasopharynx airway tolerance score [IQR]	2 [2–3]
Cough score [IQR]	1 [1–1]
SpO ₂ , median [IQR], %	99 [95–100]
RR, mean ± SD, per min	10 ± 2
Propofol dose, mg, n(%)	30,1(3.3)
Patient satisfaction score [IQR]	10 [10–10]
Bronchoscopist satisfaction score [IQR]	9 [9–10]
Aesthesiologist satisfaction score [IQR]	8 [8–8.5]
24-hour patient recall score for operation [IQR]	1 [0–1]
Patients' willingness to accept the operation again, yes, n(%)	28(93.3)

Table 5
Incidence of hypoxaemia and need for airway assistance (n = 30)

Characteristic	
Respiratory depression, n(%)	15 (50.0)
Subclinical respiratory depression	9 (30.0)
Moderate hypoxaemia	6 (20.0)
Severe hypoxaemia	0 (0)
Need for airway assistance	15 (50.0)
Stimulation	13(43.3)
Increasing oxygen delivery	0 (0)
Jaw thrust	0 (0)
Mask ventilation	1(3.3)
Mechanical ventilation	1 (3.3)
<i>*p<0.05</i>	

Figure 3 Comparison of arterial blood gas analysis before and after procedure

Table 6

Other adverse events related to the sedation (n = 30)

Item	
Adverse even, n(%)	7(23.3)
Minimal risk	0 (0)
Nausea/Vomiting	0(0)
Muscle rigidity, myoclonus	0 (0)
Agitation during recovery	0 (0)
Prolonged recovery	0 (0)
Minor risk	7 (23.3)
Airway obstruction	0 (0)
Failed sedation	0 (0)
Allergic reaction without anaphylaxis	0 (0)
Bradycardia	0 (0)
Tachycardia	2(6.7)
Hypotension	0 (0)
Hypertension	5 (16.7)
Sentinel risk	0 (0)
Cardiovascular collapse/shock	0 (0)
Cardiac arrest/absent pulse	0 (0)

Table 7
Adverse events related to oxygen
delivery system (n = 30)

Adverse event	
30 min after procedure	5(16.7)
sore throat	5(16.7)
epistaxis	0 (0)
dry mouth	0 (0)
24h after procedure	2 (6.7)
sore throat	2 (6.7)
dry mouth	0 (0)

Discussion

Through the improved sequential method, we concluded that the EC95 for remifentanyl inhibition of the stress response in fiberoptic bronchoscopy for patients with severe tracheal stenosis was 2.710 ng/ml (95% CI, 2.471–4.473 ng/ml) based on dexmedetomidine sedation and that the EC50 was 2.243 ng/mL (95% CI, 2.061–2.446 ng/mL). For all 30 patients, spontaneous breathing was retained during the diagnosis and treatment period, which improved the perioperative safety of severe patients and provided an effective and accurate MAC program for patients with severe tracheal stenosis who were undergoing fiberoptic bronchoscopy.

With the development of fiberoptic bronchoscopy technology, it has been widely used in clinical practice, and more than 500,000 bronchoscopy procedures are performed in the United States every year [13]. A large number of clinical studies have confirmed that the stress response cannot be effectively suppressed under only local anaesthesia, which may lead to choking cough or laryngeal spasm resulting in a decrease in PaO₂, aggravating the patient's dyspnoea, interrupting the operation, and even causing serious life-threatening complications such as asphyxia, massive bleeding, malignant arrhythmia and so on. Except for patients with obvious contraindications, the guidelines recommend routine sedation for all patients undergoing fiberoptic bronchoscopy [14–16]. The application of sedative medicine during fiberoptic bronchoscopy can effectively improve the patient's tolerance, reduce the choking cough during the operation and increase the patient's willingness to revisit the diagnosis and treatment without significantly increasing the related complications [15, 17, 18]. Compared with general patients, patients with severe stenosis are less tolerant to fiberoptic bronchoscopic intervention, which may improve airway

obstruction. Therefore, it is a great challenge for anaesthesiologists to provide anaesthesia management for patients with severe tracheal stenosis through fiberoptic bronchoscopy, and there is currently no recognized standardized anaesthesia management plan here or abroad [15, 19]. The level of nociceptive irritation that results from airway insertion or fiberoptic bronchoscopic procedures is similar to that of surgical incisions, and there are unique challenges to anaesthesiologists sharing the airway with the operator. The implementation of sedation and anaesthesia reduces risk, improves the comfort of patients and operators and increases the continuity and success of the procedure. In 2009, a study in China showed that 2 out of 58 hospitals routinely used general anaesthesia-assisted or controlled ventilation through laryngeal masks to complete such endoscopic diagnosis and treatment [20]. However, the depth of anaesthesia tolerated with the laryngeal mask is often deeper than that required for fiberoptic bronchoscopy, resulting in significant circulation inhibition, longer recovery time and difficulty in meeting the needs of efficient operation. The fiberoptic bronchoscope must enter the airway through the outer laryngeal mask in the mouth, which can lead to high airway pressure, air leakage and even obstruction of ventilation. There are many difficulties with respiratory management in clinical practice. Moreover, the concentration of oxygen in the airway is often too high when the laryngeal mask is ventilated, and this easily causes airway fire during laser cauterization. Compared with local and general anaesthesia, the MAC with autonomous breathing provided by the nasopharyngeal airway for oxygen has obvious advantages [21].

Sequential methods, also known as up-down methods or step-down methods, are simpler and more effective methods to study the effective concentration of drugs. The advantage of the sequential method is that it can make full use of the data provided by fewer cases and obtain results quickly and accurately, which can reduce the number of trial cases by 30% ~ 40%. Remifentanyl has a quick onset and rapid elimination, TCI makes its dose accurate and easy to adjust, and the inhibition of cardiovascular responses caused by stress can be quickly determined, which is suitable for sequential study [22, 23]. EC50 refers to half of the subjects at a particular reaction dose and can be sensitive in reflecting changes in the drug concentration and effect. EC95 refers to the effective concentration for 95% of subjects with a specific reaction. The EC50 study concentration-response relationship of a drug is more sensitive and accurate than the EC95; however, the effectiveness of the EC95 is higher, and drug-related adverse reactions may be increased because of the higher drug concentration. In the second part of this study, the EC95 of remifentanyl was used to evaluate patients' hypoxemia and other related adverse reactions, and its safety could be investigated better.

Our study showed that the incidence of respiratory depression was 50% (15/30), that of subclinical hypoxemia was 30% (9/30), that of moderate hypoxemia was 20% (6/30), and that of severe hypoxemia was 0% (0/30) among 30 patients with TCI with EC95 of remifentanyl. A total of 86.7% (13/15) of the patients with respiratory depression returned to normal by waking, one patient returned to normal by face-mask-assisted ventilation, and another patient returned to normal by laryngeal-mask mechanical ventilation. The patient with laryngeal-mask mechanical ventilation was 65 years old, weighed 46 kg, and had a height of 175 cm, a BMI of 15, hypertension, diabetes, and 75% airway stenosis. The Ramsay

sedation score was 5, the lowest SpO₂ was 85%, and SpO₂ became 100% by mask-assisted ventilation; however, breath was still not recovered. The operation was successfully completed through mechanical ventilation with the laryngeal mask, and the changes in MAP and HR did not exceed 10% of the baseline. The patient awakened 8 min after the operation, and no adverse reactions were found during the 24 h follow-up. This patient was analysed as a frail patient with hypertension and diabetes accompanied by advanced age and low body weight. The EC95 was 2.710 ng/ml (95% CI, 2.471–4.473 ng/ml) for this patient, and the depth of anaesthesia may have been too deep, leading to moderate hypoxemia. According to the response of patients to narcotic drugs, the incidence of hypoxemia can be reduced by adjusting the dosage of narcotic drugs in a timely manner. The SpO₂ % median (IQR) before and after the operation was [96 (95–97) & 99 (95–100), P < 0.05], PaO₂ (mmHg) median (IQR) values were [82.0 (77.0–86.5) & 99.6 (85.0–145.2), P < 0.05]. The increase in SpO₂ and PaO₂ during the operation may have been related to the use of the nasopharyngeal airway [24] (No. 6/7, Medis, UK); oxygen was delivered by the anaesthesia machine (6 L/min), and the APL valve was set to 30 cmHO₂. This special nasopharyngeal airway can be connected with an anaesthesia machine to supply oxygen, providing a higher concentration and more effective oxygen therapy than nasal catheters. At the same time, changes in end-expiratory carbon dioxide and respiratory rate can be continuously monitored to detect respiratory depression as early as possible and even provide an early warning before the occurrence of decreased SpO₂ to reduce the risk of clinical hypoxemic events. In the future, relevant randomized controlled studies can be designed to obtain evidence-based medicine evidence. The PaCO₂ (mmHg) median (IQR) before and after the operation was 41.5 (40.3–43.7) and 58.3 (50.7–63.0), respectively (P < 0.05), the pH median (IQR) values were [7.41 (7.39–7.43) & 7.33 (7.28–7.36), P < 0.05], and the Lac (mmol/L) median (IQR) values were [1.50 (1.20–1.80) & 1.20 (1.00–1.80), P > 0.05]. Respiratory depression that occurred during the operation led to an increase in PaCO₂, but all of these values were < 70 mmHg, which was within the range of permissible hypercapnia. The changes in pH and Lac were clinically within acceptable ranges, and the patients' circulation was stable. There was no special treatment in clinical practice. One patient was treated with propofol because performance of the operation was affected by choking cough; 30 mg of propofol was injected twice intravenously in order to complete the operation. The haemodynamics of all patients were stable at all time points during the operation, and no vasoactive drugs were used, indicating that this MAC can effectively inhibit such stress without affecting circulatory stability. The median tolerance score for nasopharyngeal airway placement was 2, the median Ramsay sedation score was 3, the median cough score was 1, the median operator-physician satisfaction score was 9, the median anaesthesiologist satisfaction score was 8, the median patient satisfaction score was 10, the median patient recall score for 24 h was 1, and the willingness of patients to accept the procedure again was 93.3%. The results show that the MAC scheme of this study provides a comfortable process of diagnosis and treatment for patients and makes the operator more comfortable completing the operation. However, the satisfaction of anaesthesiologists is not as high as that of operators and patients, which may be related to the continual focus of anaesthesiologists on the patients' breathing status. Anaesthesiologists have to spend more effort completing anaesthesia-related tasks. Other sedation-related adverse effects included an increasing heart rate and blood pressure, none of which exceeded

20% of baseline. Thirty minutes after the operation, 5 patients (16.7%) had laryngopharyngeal pain, with VAS < 3. The MAC technique of fiberoptic bronchoscopy is complicated, poses a high risk of respiratory depression and exacts a high demand from anaesthesiologists. Studies have shown that 50% of bronchoscope-related adverse events are related to sedation or (and) anaesthesia implementation, which is the main reason for the low rates of such surgical sedation and anaesthesia procedures in China [25–27]. In the process of MAC, sedation and inhibition of the airway response are mainly achieved by drugs. At present, there is no single drug that can perfectly achieve this purpose; consequently, the combined application of local anaesthesia, sedatives and opioids is clinically selected for MAC. In the UK, benzodiazepines are reported to be the most commonly used drugs (63%), followed by opioids (14%) and benzodiazepines combined with opioids (12%). The latest Australian and New Zealand censuses showed 53% use of midazolam and fentanyl. In China, benzodiazepines and/or opioids for sedation were found to be used in 44% of 58 hospitals [28–30]. Remifentanyl can effectively inhibit choking cough, is also the mainstream clinical and ultra-short-acting opioid, is effectively and rapidly metabolized, and can better and more efficiently meet the demands of clinical operation. However, the literature has reported that chest wall rigidity and bradycardia often occur [31, 32]. This study did not observe associated adverse events, which may have been related to the accurate quantitation of TCI. Minimal anaesthetic drugs were used to inhibit stress and to reduce adverse reactions, while 5 min was set to reach the plasma target concentration. Dexmedetomidine [33] is a new sedative and analgesic drug that does not easily cause respiratory depression and has obvious sedative effects. It can cause arousal sedation or cooperative sedation, is similar to normal sleep, and can reduce the dosage of opioid analgesics and adverse reactions. Therefore, in this study, the combination of remifentanyl and dexmedetomidine reduced the incidence of respiratory depression and other drug-related adverse reactions.

The shortcomings of this study are as follows: it was a prospective interventional study, not a randomized controlled study, and it did not perform comparisons with other MAC regimens. However, we believe that safe, streamlined procedures and shorter induction and recovery times are better choices for patients, anaesthesiologists, and fiberoptic bronchoscope operators.

Conclusion

In summary, our study demonstrates that the MAC of remifentanyl with spontaneous breathing provides a satisfactory sedative and analgesic effect for patients with severe tracheal stenosis during fiberoptic bronchoscopy. The EC₉₅ of remifentanyl for inhibiting the stress response of the operation was 2.710 ng/mL (95% CI, 2.471–4.473 ng/mL) and the EC₅₀ was 2.243 ng/mL (95% CI, 2.061–2.446 ng/mL). Among the 30 patients with EC₉₅ as the target concentration, 1 patient was treated with propofol to complete the operation. The stress of the remaining patients was effectively suppressed, and the satisfaction of both the operator and the patient was high. Comfortable medical treatment of the patients was realized under the MAC. The incidence of respiratory depression is 50%, and the incidence of hypoxemia is 20%; however, most of these cases can be improved by wakening, and the median SpO₂ during the operation is 99% [85–100]. MAC has high clinical safety. Nonetheless, the occurrence of

respiratory depression should be further evaluated in the next randomized controlled trial to evaluate its safety more accurately.

Abbreviations

EC:Effective concentration. TCI:Targeted controlled infusion. MAC:Monitored anesthesia care. MAP:Mean arterial pressure. HR:Heart rate. IQR: Interquartile range. VAS:Visual analogue scale. Lac:lactic acid.

Declarations

Acknowledgments

Not applicable.

Authors' contributions

Project development and design: LJM, ZY, and LX. Data collection and analysis: WW, ZYJ,SLL, LJM, and ZY. Data interpretation and manuscript writing: LJM and ZY. Manuscript revision and contribution to the knowledge content: LJM and ZY. LJM is the sponsor of the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

All data extracted in this study are included in this article.

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 was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Madan K, Mohan A, Agarwal R, et al. A survey of flexible bronchoscopy practices in India: The Indian bronchoscopy survey (2017) [J]. Lung India, 2018, 35(2): 98–107.
2. Respiratory Society of Chinese Medical Association. Expert consensus on diagnosis and treatment of benign central airway stenosis by bronchoscopic intervention [J]. Chin J Tuberculosis and Respiration, 2017, 40(06):408.
3. Respiratory and Tumor Interventional Diagnosis and Treatment Alliance of Beijing Health Promotion Association. Expert consensus on diagnosis and treatment of malignant central airway stenosis by bronchoscopy[J]. Chin J Pulmonary Diseases, 2017, 10(6): 647.
4. McGrath EE, Warriner D, Anderson P. The Insertion of Self Expanding Metal Stents With Flexible Bronchoscopy Under Sedation for Malignant Tracheobronchial Stenosis: A Single-Center Retrospective Analysis[J]. Archivos de Bronconeumología (English Edition), 2012, 48(2): 43–48.

5. Barnett AM, Jones R, Simpson G. A Survey of Bronchoscopy Practice in Australia and New Zealand[J]. *J Bronchology Interv Pulmonol*, 2016, 23: 22–8.
6. Cracco C, Fartoukh M, Prodanovic H, et al. Safety of performing fiberoptic bronchoscopy in critically ill hypoxemic patients with acute respiratory failure[J]. *Intensive Care Med*, 2013, 39(1): 45–52.
7. González Aguirre, J. E, Chavarría Martínez, et al. Bronchoscope insertion route and patient comfort during flexible bronchoscopy[J]. *The International Journal of Tuberculosis and Lung Disease*, 2015, 19(3):356–361.
8. José RJ, Shaefi S, Navani N. Sedation for flexible bronchoscopy: current and emerging evidence[J]. *Eur Respir Rev*, 2013, 22(128):106–116.
9. Hautmann H, Hetzel J, Eberhardt R, et al. Cross-Sectional Survey on Bronchoscopy in Germany - The Current Status of Clinical Practice[J]. *Pneumologie*, 2016, 70:110–116.
10. José RJ, Shaefi S, Navani N. Anesthesia for bronchoscopy[J]. *Curr Opin Anaesthesiol*, 2014, 27:453–457.
11. Pathak V, Welsby I, Mahmood K, et al. Ventilation and anesthetic approaches for rigid bronchoscopy[J]. *Ann Am Thorac Soc*, 2014, 11(4):628–634.
12. HanJU, ChoS, JeonW J, et al. The optimal effect-site concentration of remifentanyl for lightwand tracheal intubation during propofol induction without muscle relaxation [J]. *J Clin Anesth*, 2011, 23:379–383.
13. Ernst A, Silvestri GA, Johnstone D, et al. Interventional pulmonary procedures: Guidelines from the American College of Chest Physicians[J]. *Chest*. 2003, 123(5):1693–1717.
14. RJ José, Shaefi S, Navani N. Anesthesia for bronchoscopy[J]. *Curr Opin Anaesthesiol*, 2014, 27(4):453–457.
15. McCambridge AJ, Boesch RP, Mullon JJ. Sedation in Bronchoscopy: A Review[J]. *Clinics in Chest Medicine*. 2018, 39(1): 65–77.
16. Babb J, Bowie P, Brewin A, et al. British Thoracic Society guidelines on diagnostic flexible bronchoscopy[J]. *Thorax*, 2001, 56(3):i1.
17. Maguire G, Rubinfeld A, Trembath P, et al. Patients prefer sedation for fiberoptic bronchoscopy[J]. *Respirology*, 2010, 3(2):81–85.
18. Putinati S, Ballerin L, Corbetta L, et al. Patient Satisfaction With Conscious Sedation for Bronchoscopy[J]. *Chest*, 1999, 115(5):1437–1440.
19. Medford ARL, Bennett JA, Free CM, et al. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA): Applications in chest disease[J]. *Respirology*, 2010, 15(1):71–79.
20. Yang T, Hou J, Li J, et al. Retrograde light-guided laryngoscopy for tracheal intubation: clinical practice and comparison with conventional direct laryngoscopy[J]. *Anesthesiology*, 2013, 118:1059–64.
21. Cai Y, Li W, Chen K. Efficacy and safety of spontaneous ventilation technique using dexmedetomidine for rigid bronchoscopic airway foreign body removal in children[J]. *Paediatr*

- Anaesth, 2013, 23(11):1048–1053.
22. Dixon W J. Staircase bioassay: the up-and-down method[J]. *Neuroscience & Biobehavioral Reviews*, 1991, 15(1):47–50.
 23. Jin Pihuan. *Medical Statistical Methods [M].Version 2*. Shanghai: Shanghai Medical University Press, 1993:335–337.
 24. Müller M, Wehrmann T, Eckardt AJ. Prospective evaluation of the routine use of a nasopharyngeal airway (Wendl Tube) during endoscopic propofol-based sedation[J]. *Digestion*, 2014, 89(4):247–252.
 25. Liu Jin, Deng Xiaoming. 2014 edition of Chinese anesthesiology guidelines and expert consensus [M].Beijing: People's Medical Publishing House, 2014:161–169.
 26. Sarkiss M. *Anesthesia for Interventional Bronchoscopic[M] Procedures*. 2018.
 27. Goudra BG, Singh PM, Borle A, et al. Anesthesia for Advanced Bronchoscopic Procedures: State-of-the-Art Review[J]. *Lung*, 2015, Aug,193(4):453–65.
 28. Katsurada M, Izumo T. *Anesthesia for Bronchoscopy [M].// Respiratory Endoscopy*, Springer Singapore, 2017.
 29. Sarkiss M. *Anesthesia for Interventional Bronchoscopic Procedures[M].// Interventions in Pulmonary Medicine*. Springer New York, 2013.
 30. Hong KS, Choi EY, Park DA,et al.Safety and Efficacy of the Moderate Sedation During Flexible Bronchoscopic Procedure: A Systematic Review and Meta-Analysis of Randomized Controlled Trials[J]. *Medicine (Baltimore)*, 2015, 94:e1459.
 31. Lee Hyun,Choe Yeong Hun,Park Seungyong,Analgo-sedation during flexible fiberoptic bronchoscopy: comparing the clinical effectiveness and safety of remifentanil versus midazolam/propofol.[J].*BMC Pulm Med*, 2019, 19: 240.
 32. Goudra BG, Singh PM, Manjunath AK, et al. (2014) Effectiveness of high dose remifentanil in preventing coughing and laryngospasm in nonparalyzed patients for advanced bronchoscopic procedures[J]. *Ann Thorac Med*, 9:23–28.
 33. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations[J]. *Br J Anaesth*,2015, 115:171–82.

Figures

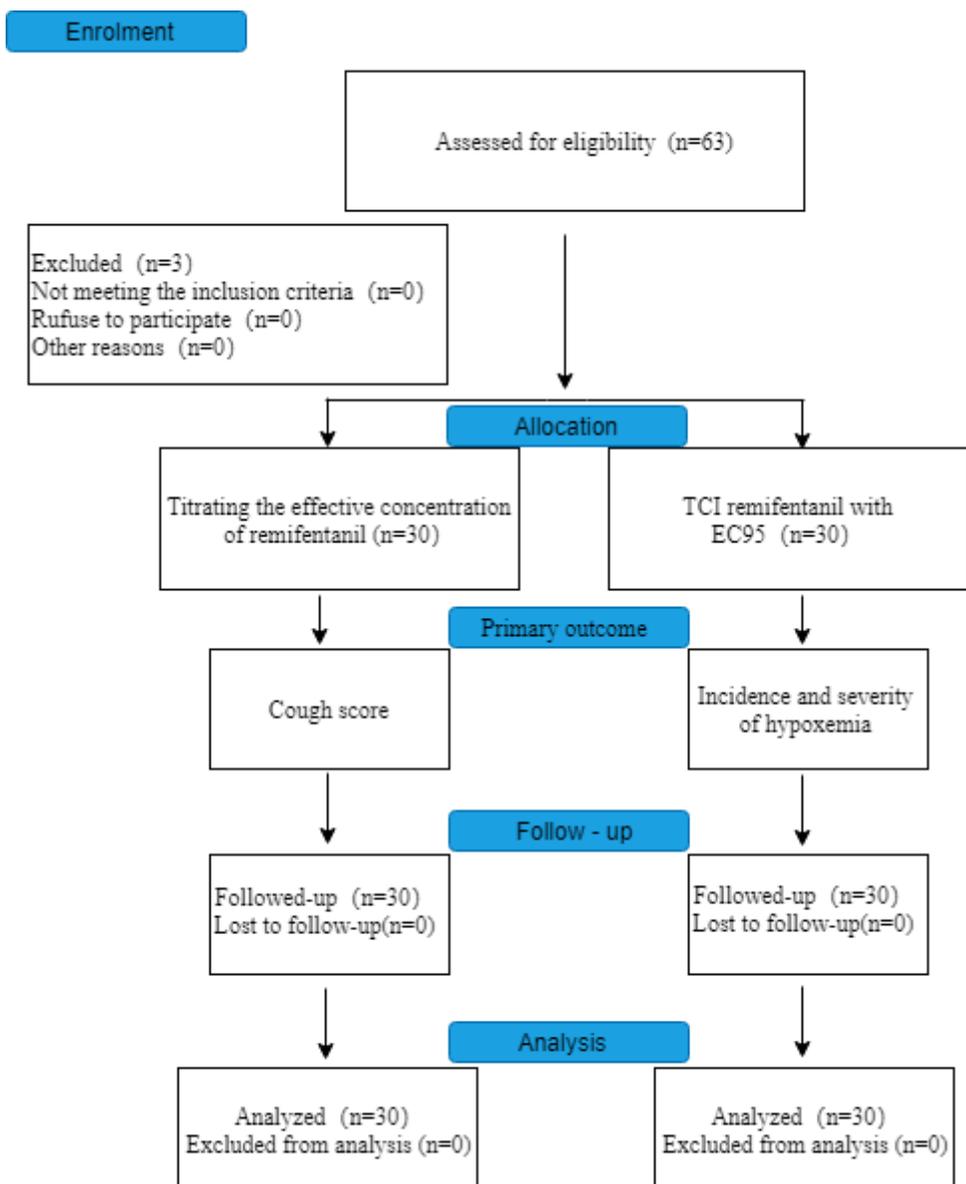


Figure 1

Consort flow diagram

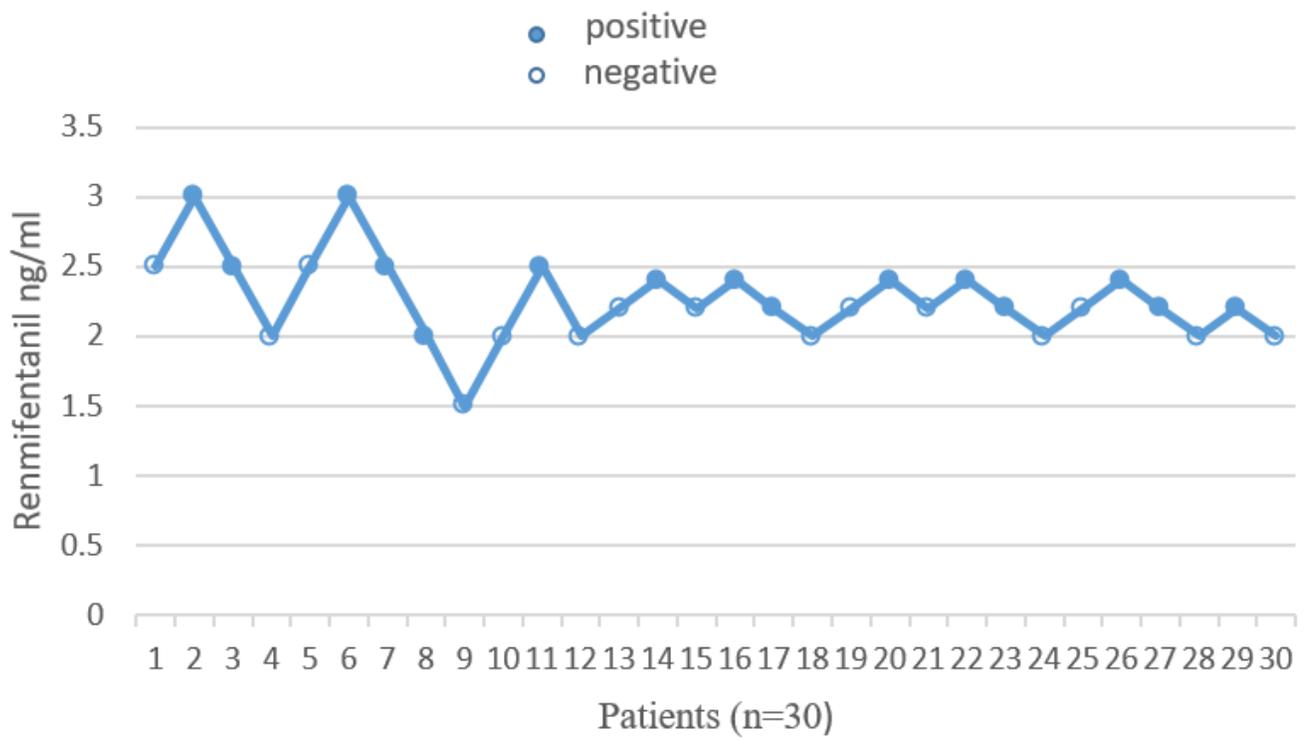


Figure 2

The response of patients to the stress of fiberoptic bronchoscopy

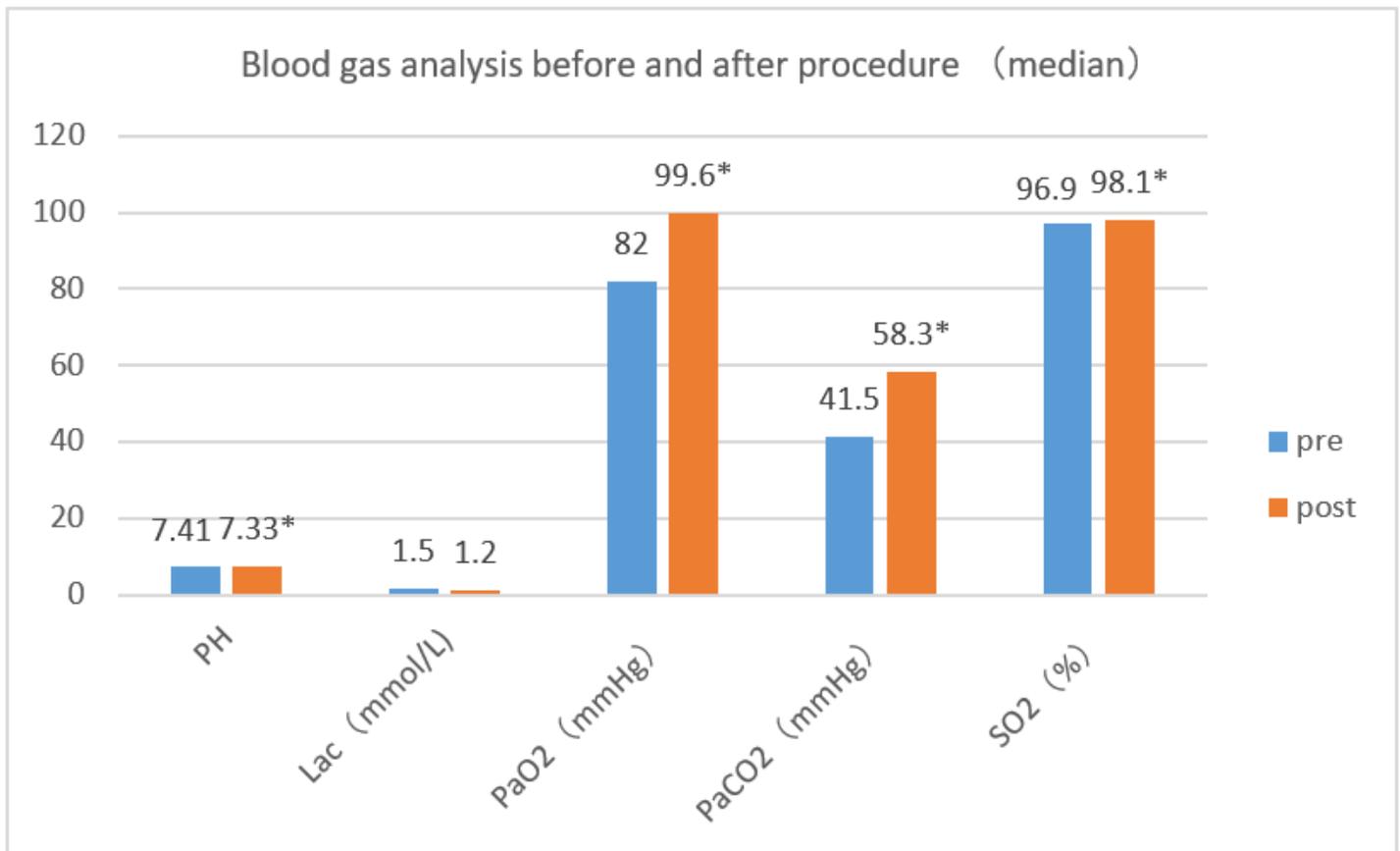


Figure 3

Comparison of arterial blood gas analysis before and after procedure