Singapore Med J 2013; 54(12): 689-694
doi:10.11622/smedj.2013243

Efficacy of target-controlled infusion of propofol and remifentanil with high frequency jet ventilation in fibre-optic bronchoscopy

Hanbing Wang[1], MD, *Chengxiang Yang*[1], MD, *Bin Zhang*[1], MD, *Yun Xia*[2], MD, *Hongzhen Liu*[1], MD, *Hua Liang*[1], MD

INTRODUCTION Sedation or anaesthesia is recommended for all patients undergoing bronchoscopy unless absolute contraindications exist. However, the widely used combination of propofol and opiates for moderate sedation (MS) in bronchoscopy results in a high incidence of hypoxaemia and a relatively high cough score during the procedure. In this study, we evaluated the efficacy and safety of target-controlled infusion (TCI) of propofol and remifentanil, together with the use of high frequency jet ventilation (HFJV), to achieve general anesthesia (GA) in diagnostic fibre-optic bronchoscopy.

METHODS A total of 92 consecutive patients scheduled for flexible bronchoscopy were randomly assigned to receive either MS using TCI-delivered propofol and remifentanil (n = 46), or GA using TCI-delivered propofol and remifentanil with HFJV (n = 46). The following were compared between the MS and GA groups: incidence of hypoxaemia, cough score, haemodynamic parameters, partial pressure of carbon dioxide in arterial blood, duration of bronchoscopy and patient satisfaction score.

RESULTS The average and minimum oxygen saturation values in the MS group were lower than those in the GA group. The MS group showed a higher incidence of hypoxaemia. There was no significant difference in the partial pressure of carbon dioxide between the two groups. Cough score and duration of the bronchoscopy were markedly lower in the GA group, and patient satisfaction score was higher in the GA group.

CONCLUSION GA, achieved via TCI-delivered propofol and remifentanil with HFJV, provides better conditions for diagnostic bronchoscopy – it decreases the occurrence of hypoxaemia, shortens the duration of bronchoscopy and increases patient satisfaction.

Keywords: bronchoscopy, target-controlled infusion, ventilation

INTRODUCTION

Of all endoscopic procedures, bronchoscopy without sedation might be one of the most painful and uncomfortable experiences. Therefore, unless absolute contraindications exist, sedation or anaesthesia is recommended for patients undergoing bronchoscopy.[1] As bronchoscopists and anaesthesiologists have to share the same airway tract, the challenge of performing bronchoscopy and maintaining normal oxygen saturation (SpO_2), while suppressing the high sympathetic response to airway stimulation, is great. Moderate sedation (MS), also known as conscious sedation, via the use of a combination of benzodiazepine and opiates is the most commonly used regimen during fibre-optic bronchoscopy.[2-4] MS is achieved with a drug-induced depression of consciousness, during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation.[5] In MS, no intervention is required to maintain a patent airway, spontaneous ventilation is adequate, and cardiovascular function is usually maintained.[5] Recently, propofol has proven effective during bronchoscopy, achieving similar results as the combined administration of midazolam and opiates in aspects such as sedation, amnesia and patient tolerance.[6] Moreover, propofol has the advantage of a shorter recovery time.[7-8]

The widely used combination of either midazolam or propofol and opiates to achieve MS for bronchoscopy has been known to result in a high incidence (~30%–50%) of hypoxaemia (i.e. SpO_2 < 90%) and a relatively high cough score.[9-11] However, the use of high frequency jet ventilation (HFJV) can provide adequate gas exchange, thus avoiding hypoxaemia without interfering with the manoeuvre of the bronchoscopist. HFJV has been successfully applied in rigid bronchoscopy and difficult airway intubation.[12-14] In light of this, the combination of general anaesthesia (GA) with HFJV might be a more acceptable regimen than conventional MS in bronchoscopy, especially with the former's lower incidence of hypoxaemia and lower cough score. To the best of our knowledge, there has been no published randomised controlled study comparing MS with GA achieved via target-controlled infusion (TCI) of propofol and remifentanil with HFJV, with respect to the incidence of oxygen desaturation, haemodynamic parameters, cough score, duration of bronchoscopy and patient satisfaction.

METHODS

This study was approved by the Research Ethics Committee (F089/2010) of Foshan Hospital, which is affiliated to Sun Yat-Sen University, China. Written informed content was obtained from

[1]Department of Anesthesiology, Foshan Hospital, Guang Dong, China, [2]Department of Anesthesiology, The Ohio State University Medical Center, Columbus, Ohio, USA
Correspondence: Dr Hua Liang, Department of Anesthesiology, Foshan Hospital, Sun Yat-Sen University, 81 North Lingnan Road, Foshan City 528000, Guang Dong Province, China. lhlh2003@126.com

all patients included in this study. A total of 92 consecutive patients, aged 20–75 years and scheduled for flexible bronchoscopy between March and May 2011, were randomly assigned (using a random computer-generated list and sealed envelope method) to receive either MS using TCI-delivered propofol and remifentanil (n = 46) or GA using TCI-delivered propofol and remifentanil with HFJV (n = 46). Patients were excluded if they had a forced expiratory volume in 1 s (FEV_1) of < 1.0 L; an American Society of Anesthesiologists (ASA) physical status higher than Class III; a body mass index of > 25 kg/m^2; moderate or severe impairment of kidney and liver function; or hypoxaemia requiring supplementary oxygen in the resting state.

All patients fasted for six hours without premedication prior to the procedure. In the preparation room, a peripheral venous line was established to administer 250 mL of Ringer's solution for a period of 20 mins before bronchoscopy. A catheter was also inserted into the radial artery to enable instant monitoring of haemodynamic changes and collect arterial blood samples to determine blood gases. Supplemental oxygen at 4 L/min was administered through a nasal cannula before sedation. In this study, all bronchoscopies were conducted by the same team, which included two nurses, one bronchoscopist, and one anaesthesiologist specialising in bronchoscopic anaesthesia and sedation. MS and GA were administered by the anaesthesiologist.

Topical anaesthesia was administered to all the patients in both the MS and GA groups prior to bronchoscopy by spraying the nostril, nasopharynx and oropharynx with 3 mL of 2% lidocaine. An additional 3 mL of 2% lidocaine was applied to the tracheobronchial tree in a spray-as-you-go manner during the procedure. In the MS group, oxygen was administered at 4 L/min via a nasal cannula throughout the bronchoscopy. Propofol was administered at a plasma target concentration of 1.5 μg/mL using a TCI pump (Graseby 3500, Smiths Medical, Watford, UK) incorporating a Diprifusor TCI system (Marsh pharmacokinetic model; AstraZeneca Pharmaceuticals, Macclesfield, Cheshire, UK). Using another syringe TCI pump (Orchestra® Base Primea, Fresenius Kabi, France) incorporating the Minto pharmacokinetic model, remifentanil was delivered at a fixed plasma concentration of 1.0 ng/mL. Based on clinical response, propofol was adjusted in increments or decrements of 0.2 μg/mL, so as to optimise the patient's bronchoscopic condition and maintain responsiveness to verbal command. Propofol administration was discontinued 2 mins before the expected end of bronchonscopy, while remifentanil infusion was maintained until the end of the procedure. If hypoxaemia occurred, the bronchoscopic manoeuvre was discontinued and mask ventilation performed until spontaneous breath recovered.

In the GA group, the initial plasma concentration of propofol was set at 4.0 μg/mL. Mask ventilation was performed immediately following loss of consciousness, and remifentanil was subsequently administered. The initial plasma concentration of remifentanil was set at 4.0 ng/mL. The tip of a Nylon catheter that was 35 cm in length and 2 mm in diameter (H795-WJ902-01A; XiHuaYi Technology Ltd, Beijing, China) was bound 8 cm from the end of the bronchoscope (Fig. 1). HFJV was achieved using a jet injector with a humidifying roller pump (TKR-400T; Jiangxi Teli Anaesthesia & Respiration Equipment Co Ltd, China), which was connected to an oxygen regulator and directly attached to the catheter (Fig. 2). The respiratory parameters were set at a frequency of 100 breaths/min, and an inspiratory/expiratory ratio of 1:3. HFJV began when the tip of the bronchoscope reached the carina. The target concentration of propofol and remifentanil were simultaneously decreased to 3.0 μg/mL and 3.0 ng/mL, respectively. During the procedure, the concentration of remifentanil was adjusted in increments or decrements of 0.5 ng/mL, according to clinical needs. Propofol administration was discontinued 2 mins before the expected end of bronchoscopy, while remifentanil infusion was maintained until the end of the procedure. Mask ventilation was continued even after bronchoscopy until effective spontaneous ventilation returned.

Fig. 1 Photograph shows the tip of the Nylon catheter bound 8 cm from the end of the bronchoscope.

Fig. 2 Photograph shows the jet injector and humidification roller pump connected to an oxygen regulator and directly attached to the Nylon catheter.

If the patient's heart rate (HR) was < 50 bpm and/or systolic blood pressure < 85 mmHg, 1 mg of dopamine was administered intravenously. In this study, tachycardia was defined as HR > 100 bpm, and hypertension was defined as > 30% increase in mean arterial pressure (MAP), compared to baseline value. The incidences of tachycardia and hypertension in the two groups were recorded. The total doses of propofol and remifentanil for each patient, the number of patients who required dopamine and the duration of bronchoscopy for each patient were recorded. Electrocardiograms, haemodynamic parameters and pulse SpO_2 levels were continually monitored throughout the entire study. MAP and HR were recorded before sedation, immediately before bronchoscopy, when the carina was reached, and 5 mins after the end of bronchoscopy. The partial pressure of carbon dioxide in arterial blood ($PaCO_2$) was analysed before sedation, 5 mins after the start of bronchoscopy, immediately after the end of bronchoscopy and 5 mins after the end of bronchoscopy. The degree of hypoxaemia was assessed using the following measurements: (a) average SpO_2; (b) lowest SpO_2; and (c) incidence of hypoxaemia during the procedure. Average SpO_2 was calculated based on the oxygen values recorded per minute. Hypoxaemia was defined as SpO_2 < 90%.[15] The time taken to regain consciousness was also recorded.

At the conclusion of the procedure, the bronchoscopist assessed patient perception of cough during the procedure using a 10-cm visual analogue scale (VAS); the 0-cm end represented 'No cough', and the 10-cm end, 'Incessant cough'. Before discharge, patients were asked to rate their satisfaction with the procedure using a 10-cm VAS; the 0-cm end represented 'Least satisfied', and the 10-cm end, 'Most satisfied'. Patients were also asked to rate their willingness to undergo repeat sedation if additional bronchoscopy was needed.

The incidence of hypoxaemia in patients who underwent fibre-optic bronchoscopy with MS has been reported to be ~30%–50%.[9-11] In patients who underwent the same procedure but with GA, this incidence is assumed to be 10%.[15] Incidence of hypoxaemia was selected as the primary outcome for sample size calculation. A total of at least 80 patients, 40 each in the MS and GA groups, was needed to achieve a power of 0.8 with a significance level (α) of 0.05 in order to detect significant differences using chi-square test. Either chi-square or Fisher's exact test was used to evaluate the differences in dichotomous variables. Normally distributed continuous parameters were analysed using unpaired *t*-test. Statistical analysis was done using the Statistical Package for the Social Sciences for Windows version 15 (SSPS Inc, Chicago, IL, USA). A p-value of < 0.05 was considered significant.

RESULTS

Patient characteristics and action taken during bronchoscopy are shown in Table I. The most common actions taken during bronchoscopy were inspection, and inspection and lavage, followed by inspection, lavage and endobronchial biopsy.

Data pertaining to the incidence and degree of hypoxaemia experienced during bronchoscopy are shown in Table II. Two patients in the MS group were excluded from analysis pertaining to hypoxaemia because the bronchial artery was injured (emergency surgery was carried out for these two patients). We found the incidence of hypoxaemia in the GA

Table I. Patient characteristics and action taken during bronchoscopy (n = 92).

Variable	No. (%)	
	MS group (n = 46)	GA group (n = 46)
Age* (yrs)	56.3 ± 11.8	57.1 ± 12.3
Male gender	27 (59)	25 (54)
Height* (cm)	164.7 ± 8.9	163.4 ± 8.0
Weight* (kg)	61.2 ± 10.6	61.5 ± 12.2
FEV_1* (L)	2.4 ± 0.7	2.4 ± 0.8
Action taken during bronchoscopy		
Inspection only	15 (33)	14 (30)
Inspection and lavage	12 (26)	13 (28)
Inspection and endobronchial biopsy	4 (9)	4 (9)
Inspection, lavage and endobronchial biopsy	9 (20)	10 (22)
Inspection and transbronchial biopsy	3 (7)	3 (7)
Inspection, lavage and transbronchial biopsy	3 (7)	2 (4)

*Data is presented as mean ± standard deviation. FEV_1: forced expiratory volume in 1 s; GA: general anaesthesia; MS: moderate sedation

Table II. Body mass index- and age-dependent reference intervals for fasting serum insulin.

Parameter	MS group (n = 44*)	GA group (n = 46)
Hypoxaemia†	15 (34.1)	1 (2.2)§
SpO_2‡ (%)		
Baseline	98.3 ± 1.4	98.3 ± 1.5
Average	93.7 ± 2.5	98.9 ± 1.5§
Minimum	91.5 ± 2.6	97.5 ± 1.7§

*Two patients were excluded because the bronchial artery was injured, and data for SpO_2 could not be obtained. †Data is presented as no. (%). ‡Data is presented as mean ± standard deviation. §p < 0.01, as compared to the MS group.
GA: general anaesthesia; MS: moderate sedation; SpO_2: oxygen saturation

Table III. Comparison of partial pressure of carbon dioxide in arterial blood ($PaCO_2$).

Time point	$PaCO_2$ (mmHg)	
	MS group (n = 42*)	GA group (n = 46)
T0	42.2 ± 3.5	41.1 ± 2.7
T1	43.1 ± 3.7	42.8 ± 3.3
T2	43.1 ± 2.9	43.2 ± 3.5
T3	42.5 ± 3.3	41.2 ± 3.0

Data is presented as mean ± standard deviation. *Blood gas analysis of blood samples taken from two patients in the MS group failed to detect $PaCO_2$. Another two patients were excluded from $PaCO_2$ analysis because the bronchial artery was injured.
GA: general anaesthesia; MS: moderate sedation; T0: before sedation; T1: 5 mins after the start of bronchoscopy; T2: immediately after bronchoscopy; T3: 5 mins after bronchoscopy

Table IV. Comparison of haemodynamic parameters during the procedure.

Time point	MS group (n = 44*)		GA group (n = 46)	
	MAP (mmHg)	HR (bpm)	MAP (mmHg)	HR (bpm)
T0	98 ± 16	84 ± 11	97 ± 16	85 ± 14
T1	94 ± 13	82 ± 15	82 ± 11	72 ± 11
T2	101 ± 15	99 ± 16†	93 ± 17	85 ± 15
T3	92 ± 15	83 ± 12	87 ± 12	82 ± 14

Data is presented as mean ± standard deviation. *Two patients were excluded because the bronchial artery was injured, and data for MAP and HR could not be obtained. †p < 0.01, as compared to T0.
GA: general anaesthesia; HR: heart rate; MAP: mean arterial pressure; MS: moderate sedation; T0: before sedation; T1: immediately before bronchoscopy; T2: at the time the carina was reached; T3: 5 mins after bronchoscopy

Table V. Comparison of outcome parameters.

Parameter	Mean ± SD	
	MS group (n = 44*)	GA group (n = 46)
Cough score	4.4 ± 1.1	1.3 ± 0.5‡
Patient satisfaction score	7.5 ± 1.5	9.4 ± 0.8‡
Patients willing to repeat procedure†	34 (77.3)	45 (97.8)‡
Patients needing dopamine†	0	1 (2.2)‡
Dose		
Propofol (mg)	117 ± 16	220 ± 25‡
Remifentanil (µg)	41 ± 7	140 ± 25‡
Duration of bronchoscopy (mins)	19.6 ± 4.4	15.8 ± 3.8§

*Two patients were excluded because the bronchial artery was injured, and their data could not be obtained. †Data is presented as no. (%).‡p < 0.01, as compared to the MS group. §p < 0.05, as compared to the MS group.
GA: general anaesthesia; MS: moderate sedation

group to be significantly lower than that in the MS group. No significant difference in the baseline SpO_2 values between the two groups was observed. However, both the average and minimum SpO_2 values in the MS group were lower than that in the GA group.

$PaCO_2$ obtained via blood gas analysis are shown in Table III. Blood gas analysis of blood samples taken from two patients in the MS group failed to detect $PaCO_2$, as the blood gas analyser could not analyse the two blood samples. No significant difference in $PaCO_2$ values between the two groups (at different time points in the procedure) was found. Haemodynamic parameters are shown in Table IV. The incidences of hypertension and tachycardia in the GA group were 1 and 2, respectively, when recorded at the time the carina was reached. These were significantly lower than the incidences of hypertension and tachycardia (8 and 14, respectively) recorded in the MS group at the same time. HR values in the MS group at the time the carina was reached were significantly increased when compared to those at baseline.

Table V compares the outcome parameters between the MS and GA groups. Cough score and the duration of bronchoscopy were markedly lower in the GA group; patient satisfaction score and the number of patients willing to repeat the procedure were higher in the GA group than the MS group. The doses of propofol and remifentanil used were higher in the GA group. There was no significant difference in the number of patients needing dopamine between the two groups. The mean time taken to regain consciousness in the GA group was 3.7 ± 1.6 mins.

DISCUSSION

Our results demonstrate that a regimen of GA achieved using TCI-delivered propofol and remifentanil, together with HFJV, could dramatically decrease the incidence of hypoxaemia in fibre-optic bronchoscopy. Moreover, the results of our study also show that GA, when compared against MS, could provide better conditions for bronchoscopy by lowering cough score and creating a more stable haemodynamic profile through effective suppression of the sympathetic response.

The advantage of using opiates in bronchoscopy is their antitussive properties.[2] The use of propofol (with or without opiates; administered intravenously via intermittent bolus or patient-controlled analgesia pump) for MS in bronchoscopy has been increasingly reported.[6,9,16] In this study, we administered propofol and remifentanil using TCI. These two intravenous medications are optimal for delivery via TCI because of their short context-sensitive half-lives.[17] When administered with a plasma target model, TCI could lead to more stable haemodynamic parameters.[18]

Currently, most patients undergoing bronchoscopy receive MS with a different regimen than the one used in the present study.[2] It is difficult for anaesthesiologists and bronchoscopists to find a balance between MS and sufficient oxygenation due to individual differences among patients. Even when combined with topical anaesthesia, many patients who are awake during the procedure inevitably experience discomfort, severe cough, dramatic haemodynamic change and hypoxaemia. Both tachycardia and myocardial ischaemia are also frequently present in elderly patients who undergo MS during bronchoscopy.[10] Given these concerns, we compared the MS (set as the control group) and GA groups. GA was achieved using TCI-delivered propofol and remifentanil, together with HFJV, in an attempt to maintain patient amnesia and more effectively suppress the airway reflex during bronchoscopy. The GA regimen was initiated with 4.0 µg/mL of propofol and 4.0 ng/mL of remifentanil, both delivered via TCI using a plasma target model. When the bronchoscope reached the carina, the target plasma concentrations of propofol and remifentanil were decreased

to 3.0 μg/mL and 3.0 ng/mL, respectively, maintaining patient amnesia and a stable haemodynamic profile. It has been demonstrated that the ED95 of the effective-site concentration of propofol at loss of consciousness is 2.0 ± 0.9 μg/mL.[19] In addition, the concentration of remifentanil was adjusted based on the clinical need to suppress airway stimulation reflex. Remifentanil is an effective antitussive medication with an ultra-short $t_{1/2}k_{e0}$, which makes it possible to achieve the desired effect site concentration instantly.[20]

Our results indicate that patients in the GA group (i.e. those who received TCI-delivered propofol and remifentanil together with HFJV) demonstrated a lower cough score and a higher satisfaction score. The GA group also had a shorter procedural duration than the MS group and a greater number of patients willing to repeat the procedure. These benefits may be attributable to the inherent characteristics of GA, in which strong airway stimulation is suppressed and patients remain amnesiac during the entire bronchoscopy. Our results also indicate that HR values in the MS group at the time the carina was reached were significantly increased compared to those at baseline. Only one patient in the GA group required the administration of dopamine; that patient's blood pressure rapidly returned to normal after dopamine was administered. The incidences of hypertension and tachycardia in the GA group were 1 and 2, respectively, when recorded at the time the carina was reached. These were significantly lower than the incidences of hypertension and tachycardia (8 and 14, respectively) recorded in the MS group at the same time. All other patients in the GA group had normal haemodynamic parameters and showed less dramatic increases in HR and MAP during late bronchoscopy. This stable haemodynamic profile in patients receiving relatively large doses of propofol and remifentanil may be explained by the use of TCI and infusion of 250 mL of Ringer's solution prior to sedation.

Hypoxaemia is the most common complication during bronchoscopy when using MS or topical anaesthesia alone. Our data showed that the incidence of hypoxaemia in the MS group was consistent with previous documentations of SpO_2 < 90% in 30%–50% of patients undergoing fibre-optic bronchoscopy with MS regimens.[9-11] Factors contributing to hypoxaemia during bronchoscopy with sedation include respiratory depression or upper airway obstruction due to excessive sedation, reflex bronchoconstriction in response to bronchoscopy or lavage (often due to inadequate sedation), persistent coughing, or endotracheal suction.[7] To address these problems, we introduced the use of HFJV and TCI-delivered intravenous propofol and remifentanil in the GA group. The feasibility of HFJV in bronchoscopy, and in cases of difficult airway management, has been reported. HFJV is usually administered using a specially devised adaptor via a laryngeal mask airway,[12] together with a bronchoscope (which forms the shared channel between the jet injection and suction),[21] or delivered through a thin nylon catheter.[22] Even though HFJV delivery takes the same route as the suction, HFJV can be interrupted when lavage or suction is needed.

Similarly, an unanchored nylon catheter placed in the trachea could be accidentally pulled out during bronchoscopy, which might lead to a risk of gastrointestinal insufflation.[23] To avoid these problems, we used a 2-mm diameter nylon catheter that had its tip bound 8 cm from the end of the bronchoscope. HFJV was initiated when the bronchoscope reached the carina, and discontinued when the tip of the bronchoscope was withdrawn above the carina. Thus, we could ensure that the tip of the catheter remained in the trachea and the lungs could be ventilated effectively. Our data demonstrates that the patients in the GA group presented a dramatically lower incidence of hypoxaemia (2.2%) than those in the MS group (34.1%). Only one patient in the GA group had SpO_2 < 90%, which had resulted from bronchial spasm and coughing due to inadequate sedation. In that case, the concentration of remifentanil was immediately increased and SpO_2 quickly returned to normal.

Blood gas analysis revealed normal $PaCO_2$ for both the GA and MS groups. Although our finding is consistent with other studies,[12,21] Hautmann et al reported an increase in $PaCO_2$ in patients receiving HFJV in interventional fibre-optic bronchoscopy, with two cases exceeding 80 mmHg.[22] However, Hautmann et al's finding could be a result of their inclusion of patients suffering from tracheal stenosis and patients who developed dyspnoea with poor FEV_1. Another study also demonstrated that HFJV could result in a rapid increase in gas retention in patients with upper airway obstruction, as passive exhalation requires patency of the proximal air tract.[23]

In the present study, GA, induced by TCI-delivered propofol and remifentanil together with HFJV, showed marked benefits in diagnostic bronchoscopy. However, our study had limitations. Firstly, patients requiring interventional procedures or those with an ASA status of Class IV and above were not included in our study. Secondly, our study was not blinded due to practical reasons. We propose that future studies be blinded and include prolonged interventional bronchoscopy.

In conclusion, GA achieved via TCI-delivered propofol and remifentanil, coupled with HFJV, is a simple and safe regimen in diagnostic bronchoscopy. This GA regimen provides better conditions for diagnostic bronchoscopy – it decreases the occurrence of hypoxaemia, shortens the duration of bronchoscopy and increases patient comfort.

ACKNOWLEDGEMENT

We wish to thank the bronchoscopist of Foshan Hospital, Sun Yat-Sen University, China, for the cooperation and invaluable assistance rendered in the assessment of cough score.

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