

The safety and efficacy of alfentanil-based induction in bronchoscopy sedation

A randomized, double-blind, controlled trial

Chung-Hsing Hsieh, MD^{a,b,d}, Ting-Yu Lin, MD^a, Tsai-Yu Wang, MD^a, Chih-Hsi Kuo, MD^a, Shu-Min Lin, MD^a, Han-Pin Kuo, MD, PhD^a, Yu-Lun Lo, MD^{a,c,*}

Abstract

Background: Alfentanil in combination with propofol produces a synergistic sedative effect in patients undergoing flexible bronchoscopy (FB). However, the use of this combination is controversial due to the risk of cardiopulmonary depression. The aim of this study was to evaluate the proper induction regimen of alfentanil in propofol target-controlled infusion for FB sedation.

Methods: One hundred seventy-three patients were assigned randomly into 5 regimens: Group 1 and 2, alfentanil 2.5 and 5 µg/kg, respectively, immediately before propofol administration; Group 3 and 4, alfentanil 2.5 and 5 µg/kg, respectively, 2 minutes before propofol administration; and Group 5, propofol administration alone to achieve the observer assessment of alertness and sedation scale 3~2. The bronchoscopists, physicians in charge of sedation, and patients were blind to the regimens. Adverse events, drug dose, induction, procedure and recovery time, cough severity, and propofol injection related pain were recorded.

Results: The patients in groups 2 and 4 required a lower dose of propofol ($P=0.031$ and 0.019 , respectively) and shorter time ($P=0.035$ and 0.010) than group 5 for induction. Patients in group 2 experienced more hypoxemia than those in group 5 during induction ($P=0.031$). The physician in charge of sedation scored a lower severity of cough in the patients in group 4 than in groups 3 and 5. There were no differences in terms of propofol injection related pain among the groups.

Conclusion: Alfentanil 5 µg/kg given immediately before propofol infusion cannot be recommended. Further study is required to define conclusions about alfentanil 2.5 and 5 µg/kg because of the low power rating of subgroup in the present study.

Abbreviations: ASA = American Society of Anesthesiologists, Ce = effect site concentration, FB = flexible bronchoscopy, FEV1 = forced expiratory volume in 1 second, FVC = forced expiratory vital capacity, OAA/S = Observer Assessment of Alertness and Sedation scale, TCI = target-controlled infusion, VAS = visual analogue scale.

Keywords: alfentanil, bronchoscopy, hypotension, hypoxemia, propofol

1. Introduction

In order to ensure patient comfort, minimize the risk, and facilitate flexible bronchoscopy (FB), the proper delivery of sedation is important, especially for complex and longer procedures.^[1] Cough, pain, and anxiety are common in patients undergoing FB, and the administration of opioids with other sedatives produces a synergistic effect on analgesia, relieving coughing, and sedation.^[2-7] Alfentanil and propofol have the

properties of fast onset and quick recovery, and they have been proven to be ideal for FB sedation providing good bronchoscopist satisfaction and patient tolerance.^[8,9] It has also been reported that alfentanil can reduce the injection pain related to propofol administration.^[10] However, the risk of cardiopulmonary depression is a critical concern because of the pharmacokinetic synergy of these drugs to suppress respiratory drive and attenuate sympathetic effects.^[11-13]

Editor: Levent Dalar.

Authorship: YLL had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conceived and designed the experiments: CHH, YLL, TYL, SML, HPK. Performed the experiments: Performed bronchoscopy and sedative procedure: CHH, YLL, TYL, CHK, TYW, CHK. Analyzed the data: CHH, YLL, TYL, HPK. Wrote the paper: CHH. Wrote the first draft of the manuscript and prepared the tables: TYL. YLL refined the subsequent drafts of the manuscript; and all contributors approved the final version.

Funding/support: This study was supported by a grant from the Chang Gung Medical Research Program (CMRPG3A1281 and CMRPG3A1282).

Trial Registration: Clinical Trials.gov Identifier: NCT01470170 <https://clinicaltrials.gov/ct2/show/NCT01470170?term=alfentanil+propofol+bronchoscopy&rank=1>.

All authors had no conflicts of interest.

^a Department of Thoracic Medicine, Chang Gung Memorial Hospital Linkou Branch, ^b Graduate Institute of Clinical Medical Sciences, College of Medicine, Chang Gung University, ^c Healthcare Center, Chang Gung Memorial Hospital, Taoyuan, ^d Department of Thoracic Medicine, Ton-Yen General Hospital, Hsinchu County, Taiwan.

* Correspondence: Yu-Lun Lo, Department of Thoracic Medicine, Chang Gung Memorial Hospital, No. 5 Fuxing St., Taoyuan, 333, Taiwan (e-mail: loyulun@hotmail.com).

Copyright © 2016 the Author(s). Published by Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Medicine (2016) 95:43(e5101)

Received: 29 May 2016 / Received in final form: 7 September 2016 / Accepted: 17 September 2016

<http://dx.doi.org/10.1097/MD.0000000000005101>

Previous studies and our work have shown that the incidence of hypoxic events during propofol sedation for FB is around 30~40%.^[9,14,15] Other studies have reported that around 14~18% of hypoxic events occur during induction.^[9,16] It would be beneficial to improve the efficacy and safety of induction; the proper regimens for induction in FB sedation, however, is an unanswered question. Various alfentanil regimens have been described for sedation in different procedures with dosages of 2.5, 4.2, 5.0, or 10 µg/kg given immediately or a few minutes before propofol administration for induction.^[8,17–22] According to pharmacokinetic properties, current evidence, and clinical experience, we used different alfentanil regimens (2.5 or 5 µg/kg) administered immediately or 2 minutes before propofol infusion in the present study to evaluate the optimal dose and timing of alfentanil in target-controlled infusion (TCI) of propofol for FB sedation to achieve a good quality of sedation with an acceptable risk.

2. Methods

This prospective, randomized, double-blind, controlled study was conducted in a tertiary center after the protocol had been approved by the Chang Gung Medical Foundation Institutional Review Board (IRB number: 99-1538A3). The clinical trial was registered to clinical trial.org (NCT01470170). Written informed consent was obtained from all participants before enrollment. Patients undergoing elective FB and sedation were screened for enrolment. The exclusion criteria were age <18 years, American Society of Anesthesiologists (ASA) physical status classification IV or V, forced expiratory vital capacity (FVC) <15 mL/kg body weight, forced expiratory volume in 1 second (FEV1) <1000 mL, or FEV1/FVC <35%, severe sleep apnea syndrome (apnea-hypopnea index >40), body mass index >42 kg/m² in males or >35 kg/m² in females, Mallampati score of 4, neurological disorders or other conditions contributing to difficulty in assessing responses, and pregnancy. Patients with a known history of allergy to the study drugs, or to eggs, soybeans, or sulfite products, were also excluded.

An intravenous catheter was placed in the forearm of the subjects for drug administration, while a nasal cannula delivered oxygen 2 L/minute. Pulse oximetry, blood pressure, heart rate, and rhythm were monitored continuously, and blood pressure was recorded every 2 minutes.

FB was performed via a nasal route by experienced bronchoscopists as previously described.^[9,16,23] Nasal, nasopharyngeal, and oropharyngeal anesthesia was achieved with nebulized 2% lidocaine. Three milliliters aliquots of 1% lidocaine were instilled over the vocal cords, carina, main bronchi, and the segment that required intervention. A well-trained physician was responsible for TCI sedation (Injectomat TIVA Agilia, Fresenius Kabi, France), monitoring the level of sedation and vital signs, and providing supportive interventions if necessary. The patients were randomly assigned following simple randomization procedures into 5 groups on the basis of a computer-generated random list (Microsoft Excel, Seattle, WA). Group 1: normal saline was given 2 minutes before the administration of propofol, and alfentanil 2.5 µg/kg was given immediately before the administration of propofol; Group 2: normal saline was given 2 minutes before the administration of propofol, and alfentanil 5 µg/kg was given immediately before the administration of propofol; Group 3: alfentanil 2.5 µg/kg was given 2 minutes before the administration of propofol, and normal saline was given immediately before the administration of propofol; Group 4: alfentanil 5 µg/kg was given 2 minutes before

the administration of propofol, and normal saline was given immediately before the administration of propofol; Group 5: normal saline was given 2 minutes and immediately before the administration of propofol as a control. The bronchoscopist, physician in charge of sedation, and patients were blinded to the patient distribution. A staff nurse responsible for the preparation of alfentanil and normal saline (placebo) was the only person who had access to the random list. Alfentanil or placebo was prepared with the same volume for each patient in a syringe with no label.

After the administration of alfentanil or placebo, the calculated effect site concentration (Ce) of induction was set at 2 µg/mL, titrated by 0.2 µg/mL in order to maintain a stable sedation level and vital signs.^[16] The Observer Assessment of Alertness and Sedation scale (OAA/S) was evaluated every 30 seconds after the patient closed their eyes. The Ce level upon reaching OAA/S 3~2 was recorded as induction Ce and set as the maintenance Ce. The duration from start of propofol infusion to OAA/S 3~2 was recorded as the induction time. If OAA/S was not achieved to 3 while the Ce was 2 µg/mL, Ce was increased by 0.2 µg/mL every 90 seconds until the OAA/S was 3~2, and the Ce was recorded as the induction Ce as well as the maintenance Ce.

During maintenance, Ce was increased by 0.2 µg/mL every 90 seconds if the patient became irritable to an extent that would interfere with the procedure. Ce was reduced by 0.2 µg/mL every 90 seconds if hypoxemia, SpO₂<90%, hypotension, mean arterial blood pressure <60 mm Hg, or systolic blood pressure <90 mm Hg occurred for any duration.

Data recorded from the beginning of induction to recovery in the bronchoscopy room included safety outcomes (hypoxemia and hypotension) and sedative outcomes (propofol dose for induction and the total procedure, induction, and recovery time). Recovery was evaluated by the time to orientation, that is, when the patients could spontaneously open their eyes, recall their date of birth, and correctly perform the finger-to-nose test.^[16] Before discharge with fully recovery whether there is pain or not related to propofol infusion was questioned to patients on a 10-cm visual analogue scale (VAS, 0: not at all; 10: most severe). Cough severity, recorded on a 10-cm VAS, of patients during FB was assessed by the bronchoscopists, physician in charge of the sedation, and patients.

2.1. Sample size

A preliminary study following the patient preparation, premedication, and sedative protocol was performed before this trial. Thirty patients undergoing FB in 5 groups were analyzed. A difference of 12% desaturation events was used to calculate the number of patients required to show the difference between the group 2 and controlled group. The selected sample size was 35 for each group for a total of 175 to yield 80% power for a 2-sided test with a significance level of 5%.

2.2. Statistical analysis

Data were expressed as number with percentage or mean with standard deviation. Normal distribution of continuous variables was tested by Kolmogorov–Smirnov test and data were analyzed by 1-way analysis of variance (ANOVA) or Kruskal–Wallis test accordingly to evaluate difference between groups, while a Bonferroni post-hoc test was performed if there was statistical significance of variables within normal distribution. Patient characteristics, complications, and symptoms were analyzed by

Chi-square test or Fisher exact test if sample size is small. A *P* value less than 0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences software package, version 13 (SPSS, Chicago, IL).

3. Results

One hundred seventy-seven patients were enrolled from October 2010 to October 2011. Among all patients who were randomly assigned, 2 patients were excluded from analysis due to incomplete questionnaire and another 2 patients were excluded from analysis due to intravenous set out. A total of 73 patients were analyzed. There were no differences between the 5 randomized groups in terms of age, gender, body mass index, ASA score, Mallampati score, smoking status, or pre-procedure vital signs (Table 1). The indications, number, and distribution of bronchial procedures per patient were comparable in each group (Table 2). The main reason for bronchoscopy was pulmonary nodules or masses (49.7%), followed by mediastinum lymphadenopathy (14.5%), and lung consolidation or infiltration (12.1%). Accordingly, the most common procedures were endobronchial ultrasound (71.1%), bronchial washing (58.4%), bronchial brushing (46.2%), and transbronchial lung biopsy (44.5%). The patients underwent multiple procedures, with approximately 50% of the patients undergoing 5 or more diagnostic and interventional bronchoscopic procedures. The average procedure time of all 5 groups was 23.1 ± 11.5 minutes.

There was a significant difference in hypoxemia during induction between the 5 groups (Table 3). Post-hoc testing further revealed that the patients in group 2 experienced more hypoxemia during induction than those in group 5 and group 1

(26% vs 3%, $P=0.008$; 26% vs 3%, $P=0.008$, respectively), suggesting that alfentanil 5 $\mu\text{g}/\text{kg}$ given immediately before propofol infusion caused significant hypoxemia during induction. There were no statistically significant differences in hypoxemia events during procedure and recovery or hypotension events during all study between groups. All events recovered spontaneously or after proper management (e.g., increasing oxygenation to 6L/minute, chin lifting, fluid challenge, or leg elevation). No other interventions (e.g., ambu-bagging, intubation or vasopressor administration), intensive care unit admission, or deaths occurred during this study.

The patients in groups 2 and 4 (alfentanil 5 $\mu\text{g}/\text{kg}$) achieved faster induction with less Ce and a lower dose of propofol than group 5 (propofol infusion alone). Propofol dosing and Ce for induction was less in Group 4 compared with group 3. There were no statistically significant differences in terms of induction time and propofol dosing between groups 1, 3 (alfentanil 2.5 $\mu\text{g}/\text{kg}$), and 5.

The patients in groups 2 and 4 (alfentanil 5 $\mu\text{g}/\text{kg}$) had a lower severity of cough than those in groups 1, 3 (alfentanil 2.5 $\mu\text{g}/\text{kg}$), and 5 according to the physicians in charge of the sedation (Table 4). However, only the patients in group 2 had a lower severity of cough than group 5 when assessed by bronchoscopists. There were no differences in cough severity between the 5 groups as judged by the patients after recovery. There were no differences in total procedure time, time to orientation (Table 3), and propofol injection related pain (Table 4) among groups.

4. Discussion

This is the first prospective, randomized, double-blind, controlled trial of using alfentanil in the induction of propofol infusion for

Table 1

Patient characteristics.

	Group 1 (34)	Group 2 (35)	Group 3 (34)	Group 4 (36)	Group 5 (34)	<i>P</i>
Age, y	60.3 \pm 11.9	60.3 \pm 15.8	58.8 \pm 13.0	60.9 \pm 13.9	62.2 \pm 11.1	0.891
Male, n (%)	19 (56)	22 (63)	17 (50)	24 (67)	21 (62)	0.651
Weight, kg	61.4 \pm 8.8	61.8 \pm 11.8	63.1 \pm 14.9	62.3 \pm 9.0	60.8 \pm 12.0	0.935
Height, m	1.61 \pm 0.1	1.62 \pm 0.1	1.62 \pm 0.1	1.63 \pm 0.1	1.61 \pm 0.1	0.925
BMI, kg/m ²	23.7 \pm 2.4	23.5 \pm 3.4	23.8 \pm 4.5	23.5 \pm 3.3	23.2 \pm 3.7	0.970
ASA score						0.726
1	19 (56)	23 (66)	23 (68)	19 (53)	24 (71)	
2	7 (21)	5 (14)	7 (21)	10 (28)	6 (18)	
3	8 (23)	7 (20)	4 (12)	7 (19)	4 (12)	
Mallampati score						0.809
1	4 (12)	6 (17)	4 (12)	5 (14)	7 (21)	
2	16 (47)	13 (37)	14 (41)	10 (28)	12 (35)	
3	14 (41)	16 (46)	16 (47)	21 (58)	15 (44)	
Regular use of opioids n (%)	1 (3)	1 (3)	1 (3)	0 (0)	0 (0)	0.722
Regular use of sedative drugs, n (%)	3 (9)	2 (6)	4 (12)	5 (14)	3 (9)	0.816
Alcohol abuse, n (%)	3 (9)	4 (11)	1 (3)	5 (14)	4 (12)	0.665
Smoking status, n (%)						0.827
Never	20 (59)	18 (48)	21 (62)	19 (53)	20 (59)	
Current	7 (21)	12 (37)	8 (23)	11 (31)	6 (18)	
Ex-	7 (21)	5 (15)	5 (15)	6 (17)	8 (23)	
Baseline vital signs						
Heart rate (beats/minute)	80.3 \pm 15.5	78.1 \pm 12.6	73.9 \pm 14.2	80.3 \pm 14.5	80.2 \pm 14.8	0.280
SBP, mm Hg	147.1 \pm 24.3	139.9 \pm 20.5	139.2 \pm 20.8	142.4 \pm 21.5	145.8 \pm 20.5	0.464
DBP, mm Hg	80.8 \pm 12.7	78.7 \pm 13.5	76.9 \pm 11.8	79.5 \pm 12.1	80.2 \pm 11.4	0.722
SpO ₂ (%)	98.8 \pm 1.5	98.6 \pm 1.5	99.0 \pm 1.4	99.2 \pm 1.3	99.1 \pm 1.5	0.544

Qualitative variables are expressed as number (percentage); quantitative variables are expressed as means \pm SD.

ASA=American Society of Anesthesiologists, BMI=body mass index, DBP=diastolic blood pressure, HR=heart rate, SBP=systolic blood pressure, SpO₂=oxyhemoglobin saturation.

Table 2**Indication for bronchoscopy and distribution of diagnostic procedures per patient.**

	Group 1 (34)	Group 2 (35)	Group 3 (34)	Group 4 (36)	Group 5 (34)	P
Indication, n (%)						
Lung nodule-s/masses	15 (44)	19 (54)	17 (50)	13 (36)	22 (65)	0.169
Mediastinum LAP-s/masses	5 (15)	5 (14)	5 (15)	8 (22)	2 (6)	0.436
Lung consolidation/ infiltration	6 (18)	4 (11)	3 (9)	4 (11)	4 (12)	0.849
Lung and mediastinum masses	2 (6)	2 (6)	4 (12)	2 (6)	2 (6)	0.821
Hemoptysis	3 (9)	2 (6)	4 (12)	2 (6)	2 (6)	0.834
Chronic cough	2 (6)	2 (6)	0 (0)	7 (19)	2 (6)	0.032
Miscellaneous	1 (3)	1 (3)	1 (3)	0 (0)	0 (0)	0.722
Diagnostic procedures, n (%)						
Bronchoscopy	31 (91)	31 (89)	33 (97)	32 (89)	33 (97)	0.467
Transbronchial lung biopsy	9 (26)	22 (63)	11 (32)	15 (42)	20 (59)	0.007
Bronchial biopsy	4 (12)	2 (6)	1 (3)	1 (3)	0 (0)	0.187
Bronchial washing	15 (44)	25 (71)	20 (59)	16 (44)	25 (74)	0.023
Bronchial brushing	9 (26)	22 (63)	13 (38)	14 (39)	22 (65)	0.004
Bronchoalveolar lavage	4 (12)	2 (6)	6 (18)	5 (14)	5 (15)	0.647
Autofluorescence bronchoscopy	10 (30)	6 (17)	9 (26)	5 (14)	8 (24)	0.494
Mini-probe EBUS	23 (68)	26 (74)	25 (74)	22 (61)	27 (79)	0.500
Real-time EBUS	8 (24)	8 (23)	9 (26)	8 (22)	5 (15)	0.752
Real-time EBUS-guided TBNA	7 (21)	4 (11)	9 (26)	8 (22)	4 (12)	0.400
Cryotherapy	1 (3)	1 (3)	2 (6)	1 (3)	0 (0)	0.718
Stent loading	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0.391
Procedures per patient (mean ± SD)	3.6 ± 1.5	4.2 ± 1.4	4.1 ± 1.5	3.5 ± 1.7	4.4 ± 1.5	0.073
Frequency of procedures, n (%)						
Inspection alone	0 (0)	1 (3)	0 (0)	5 (14)	1 (3)	0.053
2	13 (38)	6 (17)	5 (15)	9 (25)	4 (12)	0.057
3	4 (12)	2 (6)	7 (21)	2 (6)	4 (12)	0.255
4	6 (18)	4 (11)	6 (18)	5 (14)	6 (18)	0.944
5	7 (21)	19 (54)	11 (32)	13 (36)	13 (38)	0.066
6	3 (9)	3 (9)	1 (3)	1 (3)	6 (18)	0.147
7	1 (3)	0 (0)	3 (9)	1 (3)	1 (3)	0.370

Qualitative variables are expressed as number (percentage); quantitative variables are expressed as means ± SD.

EBUS = endobronchial ultrasound, TBNA = transbronchial needle aspiration.

Table 3**Bronchoscopy and sedative outcomes.**

	Group 1 (34)	Group 2 (35)	Group 3 (34)	Group 4 (36)	Group 5 (34)	P
Induction						
Ce to LOC, μg/mL	2.3 ± 0.4	2.2 ± 0.4*	2.5 ± 0.4‡	2.2 ± 0.5 ^{†,‡}	2.6 ± 0.4 ^{*,†}	0.001
Propofol dose to LOC, mg	67.8 ± 56.2	56.4 ± 29.2 [¶]	75.3 ± 37.1 [#]	54.8 ± 29.0 ^{#,**}	76.3 ± 31.9 ^{¶,***}	0.044
Induction time, s	279 ± 189	263 ± 170 [§]	374 ± 203	247 ± 183	402 ± 190 ^{§,}	0.001
Hypoxemia, n (%)	1 (3) ^{§§}	9 (26) ^{§§,}	1 (3)	6 (17)	1 (3)	0.003
Hypotension, n (%)	2 (6)	1 (4)	0 (0)	0 (0)	0 (0)	0.237
Dose of alfentanil, mg	153.5 ± 22.1	301.9 ± 65.9	154.7 ± 35.8	312.1 ± 44.3	0	—
Procedure						
Dose of propofol, mg	210.1 ± 112.7	177.8 ± 73.7 ^{††}	251.4 ± 112.7 ^{††,‡‡}	185.3 ± 103.5 ^{‡‡}	221.9 ± 89.6	0.018
Procedure time, min	23:33 ± 12:42	22:08 ± 9:18	26:17 ± 13:06	21:33 ± 12:47	22:47 ± 10:50	0.501
Hypoxemia, n (%)	13 (38)	10 (29)	16 (47)	15 (42)	18 (53)	0.306
Hypotension, n (%)	7 (21)	7 (20)	11 (32)	5 (14)	6 (18)	0.404
Recovery						
Time to orientation, min	12:35 ± 10:06	11:17 ± 6:04	14:31 ± 8:17	11:18 ± 6:47	12:42 ± 7:02	0.402
Hypoxemia, n (%)	5 (15)	2 (6)	5 (15)	4 (11)	5 (15)	0.732
Hypotension, n (%)	4 (12)	4 (11)	4 (12)	2 (6)	4 (12)	0.886

Ce = effect site concentration, LOC = loss of consciousness.

Post-hoc tests: *P = 0.016, †P = 0.003, ‡P = 0.040, §P = 0.035, ||P = 0.010, ¶P = 0.031, #P = 0.025, **P = 0.019, ††P = 0.002, ‡‡P = 0.006.

Chi-square: §§P = 0.008, |||P = 0.008.

Dose to LOC, induction hypoxemia, and dose of propofol between group 2 and 3 was P < 0.05 not shown in the table.

Qualitative variables are expressed as number (percentage); quantitative variables are expressed as means ± SD.

Hypoxemia: SpO₂ < 90%, Hypotension: (mean arterial blood pressure < 60 or systolic blood pressure < 90 mm Hg).

Table 4
Cough severity and propofol administration related pain.

	Group 1 (34)	Group 2 (35)	Group 3 (34)	Group 4 (36)	Group 5 (34)	P
Cough severity						
By physician in charge of bronchoscopy	2.4±2.2	2.0±2.1 [*]	3.4±2.22	2.4±2.0	3.6±2.5 [*]	0.009
By physician in charge of sedation	2.5±2.0	1.7±1.9 [‡]	3.7±2.5 [‡]	2.1±1.8 [‡]	3.7±2.5 ^{‡,§}	<0.001
By patient during procedure	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	—
By patient post-procedure	1.1±2.0	0.5±0.9	1.6±2.4	1.1±1.8	1.1±1.8	0.278
Injection site pain n (%)	7 (21)	6 (17)	11 (33)	7 (19)	11 (33)	0.394

Post-hoc tests (Bonferroni): ^{*}P=0.031, [‡]P=0.002, [§]P=0.041, ^{||}P=0.029.

Cough severity scored by the physician in charge of sedation between group 2 and 3 was P<0.05 not shown in the table.

Qualitative variables are expressed as number (percentage); quantitative variables are expressed as means±SD.

^{||} Assessed by 10 cm visual analogue scale (0: not at all; 10: most severe).

FB sedation. The results demonstrated that alfentanil 5 µg/kg given immediately or 2 minutes before propofol infusion achieved faster induction with less dose of propofol and better cough profile evaluated by physicians performing sedation than control group 5, but alfentanil 5 µg/kg given immediately propofol infusion caused significant hypoxemia during induction than control group. Therefore, alfentanil 5 µg/kg given immediately propofol infusion cannot be recommended. Alfentanil 5 µg/kg given 2 minutes before propofol infusion was the possible potential induction regimen for TCI propofol infusion in FB sedation.

The aim of the present study was to ascertain the regimen of alfentanil in propofol infusion for FB sedation to achieve an acceptable benefit and risk ratio, and an induction regimen of alfentanil 5 µg/kg (group 2 and 4) was found to provide a better sedative profile with regard to induction time, propofol dose of induction, and cough severity, although the benefit in coughing was not significant when assessed by the patients, probably because of the amnesia effects of sedation. Shifting the administration of alfentanil to 2 minutes before propofol infusion (group 4) ameliorated hypoxemia.

Compared with group 5 (propofol alone), group 4 used a lower amount of propofol by 10~20mg and saved 2 minutes in induction, implicating the synergistic effect between alfentanil 5 µg/kg and propofol infusion. This effect was also observed in the induction time. A recent study reported that alfentanil in combination with propofol for FB sedation did not improve the quality of sedation compared with propofol alone, although this combination resulted in greater respiratory depression.^[11] However, the sedative protocol was fundamentally different from the present study, in that they used a patient-controlled sedation device with a mixture of alfentanil and propofol. The sedative level was relatively shallow because the drugs were administered according to the patients' self-perception of discomfort, and the majority of patients underwent 2 procedures. Most importantly, alfentanil was given in every bolus, which is different from our study and may be the reason for the higher incidence of hypoxemia in sedation with both alfentanil and propofol than in sedation with propofol alone.

The interaction between propofol and alfentanil is complicated at both pharmacokinetic and pharmacodynamics levels.^[6] Alfentanil and propofol can decrease the clearance of each other, and alfentanil has been shown to decrease the amount of propofol needed for induction of anesthesia in a synergistic manner.^[2,3,24] The duration of induction for FB sedation is narrow, and we designed the present regimens on the basis of our experience and relevant pharmacokinetic evidence of alfentanil and propofol.^[9,16] Computer simulation has shown that the time to peak effect after a

bolus of alfentanil is around 3 to 4 minutes.^[6] The time to peak effect of propofol in the Schnider model of TCI is 1.69 minutes after the initial bolus.^[25] Administering alfentanil 2 minutes before propofol infusion will cause the peak effect of both drugs to occur at approximately the same time, which may then lead to a maximal synergistic effect. Administering alfentanil immediately before propofol has been reported in many studies on procedures for sedation.^[9,22,26] Various doses of alfentanil have also been used in sedative bronchoscopy in previous reports, such as 2.5, 4.2, 5.0, and 10 µg/kg.^[8,17-20,22] We chose 2.5 and 5 µg/kg in the present study, as a high risk of hypoxemia has been reported with alfentanil 10 µg/kg.^[22,27]

There was no significant difference in outcomes between alfentanil 2.5 and 5 µg/kg. A possible reason is that the power in subgroup analysis is not enough and further prospective study is required to define conclusions about induction regimen of alfentanil 2.5 and 5 µg/kg in FB sedation.

Under the blinded condition, the bronchoscopists scored lower cough severity in group 2 than in group 5. In addition, the physicians in charge of sedation also scored lower cough severity in group 4 than in groups 3 and 5. The reason for this difference is probably due to the bronchoscopists focusing more on completing the complicated procedures, and the physicians in charge of bronchoscopy tending to observe the patients more thoroughly. Furthermore, from the point of view of the patients, cough severity was excellent in all 5 groups. Therefore, our findings confirm that this sedation regimen offers a high degree of satisfaction.

There were no differences in terms of the incidence of propofol injection related pain among the 5 groups. This may be because the dose of alfentanil was not high enough to suppress pain. In previous studies, 15 µg/kg~1mg alfentanil was used for propofol-induced pain; however, this increases the risk of hypoxemia during FB sedation.^[10,27]

The present study has several limitations. We used TCI for propofol administration because TCI integrates individual variables and then provides precise pharmacokinetic control to achieve a steady plasma concentration and improved hemodynamic stability.^[16,28] However, TCI is not always available in a clinical setting. We focused on the optimal regimen for induction, and the outcomes were mostly related to induction. During the minutes before achieving the desired sedation, differences between different administration protocols, for example, TCI, manually controlled infusion, or bolus of propofol may not be too substantial. Despite these limitations, our findings provide scientific evidence with regard to sedative induction for FB sedation. We hope that this study prompts further research to improve the safety and efficacy of FB sedation.

In conclusion, induction with alfentanil 5 µg/kg given immediately before propofol TCI sedation for bronchoscopy is risky particular for hypoxemia. Further study is required to define conclusions about the induction regimens of alfentanil 2.5 and 5 µg/kg.

Acknowledgment

The authors thank Yu-Jr Lin, PhD, for statistic consultation.

References

- [1] Jose RJ, Shaefi S, Navani N. Sedation for flexible bronchoscopy: current and emerging evidence. *Eur Respir Rev* 2013;22:106–16.
- [2] Mertens MJ, Vuyk J, Olofsen E, et al. Propofol alters the pharmacokinetics of alfentanil in healthy male volunteers. *Anesthesiology* 2001;94:949–57.
- [3] Mertens MJ, Olofsen E, Burm AG, et al. Mixed-effects modeling of the influence of alfentanil on propofol pharmacokinetics. *Anesthesiology* 2004;100:795–805.
- [4] Diette GB, White PJr, Terry P, et al. Quality assessment through patient self-report of symptoms prefiber optic and postfiber optic bronchoscopy. *Chest* 1998;114:1446–53.
- [5] Poi PJ, Chuah SY, Srinivas P, et al. Common fears of patients undergoing bronchoscopy. *Eur Respir J* 1998;11:1147–9.
- [6] Lichtenbelt BJ, Mertens M, Vuyk J. Strategies to optimise propofol-opioid anaesthesia. *Clin Pharm* 2004;43:577–93.
- [7] Lysakowski C, Dumont L, Pellegrini M, et al. Effects of fentanyl, alfentanil, remifentanyl and sufentanyl on loss of consciousness and bispectral index during propofol induction of anaesthesia. *Br J Anaesth* 2001;86:523–7.
- [8] Hwang J, Jeon Y, Park HP, et al. Comparison of alfentanil and ketamine in combination with propofol for patient-controlled sedation during fiberoptic bronchoscopy. *Acta Anaesthesiol Scand* 2005;49:1334–8.
- [9] Lo YL, Lin TY, Fang YF, et al. Feasibility of bispectral index-guided propofol infusion for flexible bronchoscopy sedation: a randomized controlled trial. *PLoS One* 2011;6:e27769.
- [10] Iyilikci L, Balkan BK, Gokel E, et al. The effects of alfentanil or remifentanyl pretreatment on propofol injection pain. *J Clin Anesth* 2004;16:499–502.
- [11] Yoon HI, Kim JH, Lee JH, et al. Comparison of propofol and the combination of propofol and alfentanil during bronchoscopy: a randomized study. *Acta Anaesthesiol Scand* 2011;55:104–9.
- [12] Ebert TJ. Sympathetic and hemodynamic effects of moderate and deep sedation with propofol in humans. *Anesthesiology* 2005;103:20–4.
- [13] Mildh LH, Scheinin H, Kirvela OA. The concentration-effect relationship of the respiratory depressant effects of alfentanil and fentanyl. *Anesth Analg* 2001;93:939–46.
- [14] Clark G, Licker M, Younosian AB, et al. Titrated sedation with propofol or midazolam for flexible bronchoscopy: a randomised trial. *Eur Respir J* 2009;34:1277–83.
- [15] Stolz D, Kurer G, Meyer A, et al. Propofol versus combined sedation in flexible bronchoscopy: a randomised non-inferiority trial. *Eur Respir J* 2009;34:1024–30.
- [16] Lin TY, Lo YL, Hsieh CH, et al. The potential regimen of target-controlled infusion of propofol in flexible bronchoscopy sedation: a randomized controlled trial. *PLoS One* 2013;8:e62744.
- [17] Greig JH, Cooper SM, Kasimbazi HJ, et al. Sedation for fibre optic bronchoscopy. *Respir Med* 1995;89:53–6.
- [18] Passot S, Servin F, Allary R, et al. Target-controlled versus manually-controlled infusion of propofol for direct laryngoscopy and bronchoscopy. *Anesth Analg* 2002;94:1212–6. table of contents.
- [19] Knolle E, Oehmke MJ, Gustorff B, et al. Target-controlled infusion of propofol for fiberoptic intubation. *Eur J Anaesthesiol* 2003;20:565–9.
- [20] Miner JR, Gray R, Delavari P, et al. Alfentanil for procedural sedation in the emergency department. *Ann Emerg Med* 2011;57:117–21.
- [21] Kestin IG, Chapman JM, Coates MB. Alfentanil used to supplement propofol infusions for oesophagoscopy and bronchoscopy. *Anaesthesia* 1989;44:994–6.
- [22] Yu AL, Critchley LA, Lee A, et al. Alfentanil dosage when inserting the classic laryngeal mask airway. *Anesthesiology* 2006;105:684–8.
- [23] Ni YL, Lo YL, Lin TY, et al. Conscious sedation reduces patient discomfort and improves satisfaction in flexible bronchoscopy. *Chang Gung Med J* 2010;33:443–52.
- [24] Vuyk J, Engbers FH, Burm AG, et al. Pharmacodynamic interaction between propofol and alfentanil when given for induction of anaesthesia. *Anesthesiology* 1996;84:288–99.
- [25] Absalom AR, Mani V, De Smet T, et al. Pharmacokinetic models for propofol—defining and illuminating the devil in the detail. *Br J Anaesth* 2009;103:26–37.
- [26] Miner JR, Gray RO, Stephens D, et al. Randomized clinical trial of propofol with and without alfentanil for deep procedural sedation in the emergency department. *Acad Emerg Med* 2009;16:825–34.
- [27] Kwak HJ, Min SK, Kim JS, et al. Prevention of propofol-induced pain in children: combination of alfentanil and lidocaine vs alfentanil or lidocaine alone. *Br J Anaesth* 2009;103:410–2.
- [28] Struys MM, De Smet T, Depoorter B, et al. Comparison of plasma compartment versus two methods for effect compartment-controlled target-controlled infusion for propofol. *Anesthesiology* 2000;92:399–406.