Patient-controlled Sedation During Flexible Bronchoscopy
A Randomized Controlled Trial

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Background: **Patient-controlled sedation (PCS) is a documented method for endoscopic procedures considered to facilitate early recovery. Limited data have been reported, however, on its use during flexible bronchoscopy (FB).**

Methods: **This study hypothesized that PCS with propofol during FB would facilitate early recovery, with similar bronchoscopist and patient satisfaction compared with nurse-controlled sedation (NCS) with midazolam. A total of 150 patients were randomized 1:1:1 into a control group (premedication with morphine-scopolamine and NCS with midazolam), PCS-MS group (premedication with morphine-scopolamine and PCS with propofol), and PCS-G group (premedication with glycopyrronium and PCS with propofol).**

Results: **The procedures included transbronchial biopsy, transbronchial needle aspiration, cryotherapy/biopsy, and/or multistation endobronchial ultrasound. FB duration values in median (range) were 40 (10 to 80), 39 (12 to 68), and 44 (10 to 82) minutes for the groups NCS, PCS-MS, and PCS-G, respectively. An overall 81% of the patients in the combined PCS groups were ready for discharge (modified Post Anaesthetic Discharge Scoring System, score 10) 2 hours after bronchoscopy compared with 40% in the control group ($P < 0.0001$). Between PCS groups, 96% of the PCS-G group patients were ready for discharge compared with 65% in the PCS-MS group ($P = 0.0002$) at 2 hours. Bronchoscopists' and patients' satisfaction scores were high in all groups. Postdischarge quality scores showed no differences among the groups.**

Conclusion: **PCS with propofol during FB is feasible, as it shortened recovery time without compromising procedure conditions for bronchoscopists or patients. A rapid postsedation stabilization of vital signs facilitates surveillance before the patient leaves the hospital.**

Key Words: analgesia, patient-controlled, conscious sedation, anesthesia, intravenous, bronchoscopy, propofol

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Flexible bronchoscopy (FB) is a common outpatient diagnostic and therapeutic procedure for various pulmonary diseases. According to current UK and US guidelines,[1,2] sedation is offered to improve the procedure's feasibility and increase patient comfort and tolerance. In connection with outpatient endoscopy procedures, rapid recovery is of great importance to increase turnover without affecting patient safety and procedure feasibility.

Benzodiazepines with or without opioids along with propofol are commonly used for sedation during FB. They show equivalent efficacy[3,4] and have similar risk profiles,[3–7] but benzodiazepines have a slower onset of action[3,4] and result in prolonged recovery.[3–7] Propofol is favored on the basis of its higher patient satisfaction[7] and procedure feasibility for bronchoscopists.[4]

Patient-controlled sedation (PCS) allows the patients to self-administer the sedative, as needed. Use of this method has been increasing for endoscopic procedures; PCS is considered safe in terms of cardiorespiratory adverse events and has shown more rapid recovery times when compared with traditional nurse-controlled sedation (NCS).[8,9] PCS with propofol alone results in faster discharge than midazolam during NCS[9] or propofol administered by a nurse anesthetist.[10] To our knowledge, only one study has evaluated PCS during FB; however, it was combined with background infusion and used as a combination of propofol and ketamine/alfentanil.[11] On the basis of reports using PCS

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with propofol alone for other types of endoscopic procedures,[9] we suggest it may be a promising alternative for FB for providing reliable procedure conditions and rapid recovery.

The present study evaluates PCS during FB. We hypothesized that propofol-only PCS would facilitate early recovery, with similar ease of procedure and patient satisfaction compared with a standard regimen of NCS with midazolam.

MATERIALS AND METHODS

Enrollment and Eligibility

The study was conducted following the principles of the amended Declaration of Helsinki at the Department of Pulmonary Medicine, Linköping University Hospital, from April 2016 to May 2017. The Regional Ethics Review Board (2015/481-31) and the Swedish Medical Products Agency (5.1-2016-686) approved the study, and it was overseen by an independent monitor. The study was registered at the EU Clinical Trials Register (2015-005274-38). Adult patients scheduled for outpatient FB were assessed for eligibility during the preprocedural preparation, and all participants provided written informed consent. The procedures included transbronchial biopsy, transbronchial needle aspiration, cryotherapy/biopsy, and/or multistation endobronchial ultrasound. No electromagnetic navigation was performed, but all procedures used the miniprobe and/or fluoroscopy. No onsite pathology was used. Exclusion criteria were a positive pregnancy test, contraindication for the study drugs, functional disability, and cognitive impairment or language difficulties affecting PCS device operation.

Study Design

We designed a prospective, randomized, controlled trial with 3 parallel groups to compare propofol PCS with NCS with midazolam. The primary outcome was the proportion of patients ready for discharge at 2 hours after FB [with a modified Post Anaesthetic Discharge Scoring System (PADSS) score of 10], and secondary outcomes were ease of procedure, patient satisfaction in connection with FBB, and quality of postdischarge recovery. We also assessed patient safety with regard to depth of sedation, cardiopulmonary adverse events, and interventions during the procedures to stabilize vital signs.

Randomization

The patients were randomized consecutively on the day of the FB into 3 arms (1:1:1) using sealed opaque envelopes as follows: control group: subcutaneous premedication with morphine-scopolamine [Morfin-Skopolamin Meda (10+0.4) mg/mL, Meda AB, Solna, Sweden] and NCS with intravenous (IV) midazolam (Midazolam Accord 1 mg/mL, Accord Healthcare AB, Solna, Sweden); PCS-MS group: subcutaneous premedication with morphine-scopolamine and sedation with IV propofol (Recofol 10 mg/mL, Algol Pharma AB, Kista, Sweden) using PCS; and PCS-G group: intramuscular premedication with glycopyrronium (Robinul 0.2 mg/mL, Meda AB) and sedation with IV propofol via PCS.

Patients followed European anesthetic guidelines for preoperative fasting.[12] The bronchoscopist was blinded to the premedication, and it was administered by the bronchoscopic team as follows: control group and PCS-MS group, morphine-scopolamine by age (18 to 54 y, 1.0 mL; 55 to 65 y, 0.75 mL; above 65 y, 0.5 mL), and PCS-G group, glycopyrronium 0.2 mg. All patients were started on ipratropium (0.5 mg; Atrovent 0.25 mg/mL, Boehringer Ingelheim AB, Stockholm, Sweden) and lidocaine (120 mg; Lidokainhydroklorid APL 40 mg/mL, Apotek Produktion & Laboratorier AB, Kungens Kurva, Sweden) by nebulized inhalation ~30 minutes before the procedure.

Study Protocol

The procedure began with the initiation of sedation. Patients in the control group were cared for by the bronchoscopic team and received an initial dose of 1.25 mg of midazolam and, when necessary, repeated doses of 1.25 mg, according to the type of procedure or bronchoscopist request. The patients in the PCS-MS and PCS-G groups used a PCS device (T34L PCA, CME Ltd., Lichtenstein, Germany). Before premedication was administered, comprehensive information was provided on how to operate the device. By pressing a button, patients could self-administer a bolus of 5 mg of propofol (0.5 mL) without lockout periods. The delivery time was ~8 seconds, with an estimated maximum of 35 mg of propofol/min if the patient were to repeatedly press the button for boluses. Before bronchoscope insertion, and every 5 minutes during the procedure, patients using PCS were encouraged to utilize the device to maintain an Observer's Assessment of Alertness/Sedation scale (OAA/S) sedation level of 2 (see below, "Sedation level assessment").

Parallel to sedation initiation, the bronchoscopist administered lidocaine (Xylocain 2%,

AstraZeneca AB, Södertälje, Sweden) in the nostril and to the oropharynx, vocal cords, and trachea/bronchi (spray-as-you-go technique; Lidokain Mylan 20 mg/mL, Mylan Hospital AS, Oslo, Norway). The bronchoscopist could request additional topical anesthetics or pain relief (alfentanil; Rapifen 0.5 mg/mL, Janssen-Cilag AB, Solna, Sweden), and more sedatives [midazolam (control group)] administered by the bronchoscopic team, or propofol (PCS-MS and PCS-G groups) administered by the nurse anesthetist, for especially demanding episodes. The procedure was considered complete upon removal of the bronchoscope.

The patients in the control group were cared for in the department of pulmonary medicine, and all requisite sedation and reversing drugs were given in accordance with standard protocol.

Vital Sign Monitoring

The oxygen saturation (SpO_2), heart rate (HR), arterial noninvasive blood pressure (NIBP), and respiratory rate (RR), were monitored during the procedure by the bronchoscopic team (control group) or nurse anesthetist (PCS groups), with an anesthesiologist immediately available by pager, and postprocedurally by the bronchoscopic team (all groups). Swedish nurse anesthetists hold a graduate diploma in specialist nursing and independently induce, maintain, and conclude general anesthesia with supervision from an anesthesiologist. Vital signs were recorded every 5 minutes perprocedurally and every 15 minutes postprocedurally for up to 4 hours after FB. Hypoxemia was defined as $SpO_2 < 90\%$, hypotension as NIBP <90 mm Hg, bradycardia as HR < 40 beats/min, and respiratory depression as RR < 8 breaths/min. During hypotension events with two repeated measurements or at bradycardia, 5 mg of ephedrine or 0.5 mg atropine was administered intravenously, respectively. All patients had an open airway with spontaneous breathing and received supplementary oxygen by nasal catheter after premedication administration and during the procedure, and, if needed, postprocedurally. Upon desaturation, patients were encouraged to take deep breaths; if desaturation continued, oxygen pressure was increased. During episodes of semiobstructed or obstructed airway, appropriate interventions were undertaken. Appropriate rescue equipment was immediately available if intubation was required.

Sedation Level Assessment

Sedation level was assessed every 5 minutes perprocedurally according to the OAA/S scale.[13] Scores were as follows: "Does not respond to mild prodding or shaking" (1), "Responds only after mild prodding or shaking" (2), "Responds only after name is called loudly and/or repeatedly" (3), "Lethargic response to name spoken in normal tone" (4), and "Responds readily to name spoken in normal tone" (5).

Procedure Assessment

The bronchoscopist assessed the ease of procedure with regard to cough, airway secretion, feasibility, and patient movement. The patients assessed their overall satisfaction before discharge. Both assessments used a Likert scale of "very dissatisfied" (1), "dissatisfied" (2), "neither dissatisfied nor satisfied" (3), "satisfied" (4), or "very satisfied" (5).

Recovery Assessment

The modified PADSS[14] assesses patient recovery according to 5 categories, each with scores from 0 to 2 and a maximum total score of 10 (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/LBR/A185). Patients with a PADSS score of 10 were deemed ready for discharge. Patients with a PADSS score >9 at 4 hours after the procedure were transferred to the ward for overnight monitoring. Patients filled out 2 self-rated questionnaires for assessment of recovery: the Post-Discharge Surgical Recovery scale (PSR),[15] a 12-item questionnaire assessing health status and activity after discharge, with a score range of 10 to 100 (higher scores indicating positive postoperative recovery), filled out the day of the procedure at 8 PM, and the Quality of Recovery-23 (QoR-23),[16] assessing emotional state, physical comfort, and physical independence after day surgery, with a maximum total score of 115 (higher scores indicate higher quality of recovery), filled out the day after the procedure.

Statistical Analysis

Retrospective data for midazolam sedation and a 2015 pilot study of 10 patients using PCS were used for sample-size analysis. With a power of 80% and $P < 0.05$, we calculated sample sizes for the groups (control vs. PCS) with an enrollment ratio of 1:2. We hypothesized that 75% of the PCS patients and 50% in the control group would reach a PADSS score of 10 after 2 hours. Sample size calculation resulted in 42 for the control group and 84 for the PCS groups. With potential dropout cases, we rounded up the sample size to 50 for the control group and 100 for the PCS groups. After study completion, the administered premedication

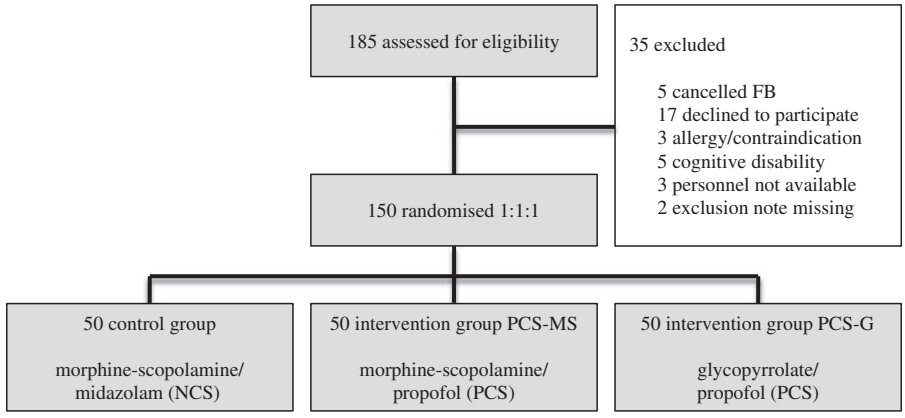

FIGURE 1. Flowchart. FB indicates flexible bronchoscopy; NCS, nurse-controlled sedation; PCS, patient-controlled sedation; PCS-MS, patient-controlled sedation with propofol and morphine-scopolamine as premedication; PCS-G, patient-controlled sedation with propofol and glycopyrronium as premedication.

was unblinded, and the groups were compared. The groups were compared using a planned comparison. First, the control group was compared with the combined 2 PCS groups. Second, the PCS-MS group was compared with the PCS-G group. Quantitative data were assessed with the Student *t* test or the Mann-Whitney *U* test. A χ^2 test or the Fischer exact test was used for categorical data. Results are presented as median (interquartile range), median (minimum-maximum), or number of patients (%).

RESULTS

Of 185 patients screened for inclusion, 150 were randomized 1:1:1 into the 3 groups (Fig. 1). The patients' and procedure characteristics were similar among groups (Table 1).

Significantly more patients in the PCS groups (81%) were ready for discharge (PADSS 10) 2 hours after the procedure when compared with the control group (40%; $P < 0.0001$; Table 2). A difference also was found between the PCS-G (96%) and PCS-MS groups (65%; $P = 0.0002$;

TABLE 1. Patient and Procedure Characteristics

	A		B	
	Control (n = 50)	**PCS (n = 100)**	**PCS-MS (n = 50)**	**PCS-G (n = 50)**
Age (y)	70 (33-83)	68 (25-89)	69 (25-86)	68 (25-89)
Weight (kg)	73 (44-142)	74 (41-114)	72 (46-106)	75 (41-114)
BMI (kg/m^2)	25 (16-46)	26 (15-39)	25 (17-33)	26 (15-39)
Sex (M/F)	28/22	50/50	28/22	22/28
ASA classification				
I	13 (26)	23 (23)	16 (32)	7 (14)
II	12 (24)	34 (34)	15 (30)	19 (38)
III	25 (50)	43 (43)	19 (38)	24 (48)
Type of procedure				
Bronchoscopy*	27 (54)	49 (49)	25 (50)	24 (48)
Bronchoscopy with EBUS†	22 (44)	46 (46)	23 (46)	23 (46)
Only EBUS	1 (2)	5 (5)	2 (4)	3 (6)
Duration procedures (min)				
All procedures	40 (10-80)	41 (10-82)	39 (12-68)	44 (10-82)
Bronchoscopy*	30 (10-65)	30 (10-66)	30 (12-66)	30 (10-60)
Bronchoscopy with EBUS†	52 (25-80)	48 (16-82)	44 (16-68)	52 (23-82)
Only EBUS	55 (55-55)	42 (27-54)	42 (42-42)	45 (27-54)

Part A displays the control group and the 2 PCS groups combined.
In part B, the PCS groups are separated.
Data are presented as median (minimum-maximum) or as the number of patients (%).
*Including TBNA, TBB, and cryotherapy/biopsy.
†Including TBNA/TBB and multistation EBUS in one session.
ASA indicates American Society of Anesthesiologists; BMI, body mass index; EBUS, endobronchial ultrasound; PCS-G, patient-controlled sedation with propofol and glycopyrrolate as premedication; PCS-MS, patient-controlled sedation with propofol and morphine-scopolamine as premedication; TBB, transbronchial biopsy; TBNA, transbronchial needle aspiration.

TABLE 2. Peroperative and Postoperative Data on Drugs, Ease of Procedure, Patient Satisfaction, and Recovery

	(A) Control vs. PCS			(B) PCS-MS vs. PCG-G		
	Control	**PCS**	***P***	**PCS-MS**	**PCS-G**	***P***
Midazolam (mg)	3.75 (1.25-8.75)	—	—	—	—	—
Propofol (mg) (given by patient)	—	200 (55-466)	—	160 (55-315)	241 (80-466)	< 0.0001
Lidocaine (mg)	300 (180-560)	280 (180-480)	0.011	270 (180-480)	280 (200-460)	0.389
Alfentanil	5 (10)	18 (18)	0.200	8 (16)	10 (20)	0.603
Flumazenil	27 (54)	0 (0)	< 0.0001	0 (0)	0 (0)	—
Naloxone	17 (34)	0 (0)	< 0.0001	0 (0)	0 (0)	—
Ease of procedure (score)						
Bronchoscopy*						
Patient cough	4 (1-5)	4 (1-5)	0.836	4 (1-5)	4 (1-5)	0.669
Bronchial secretion	4 (2-5)	4 (2-5)	0.464	4 (2-5)	4 (2-5)	0.957
Feasibility	5 (2-5)	4 (1-5)	0.739	4 (1-5)	4 (2-5)	0.674
Patient movement	5 (2-5)	5 (1-5)	0.820	4 (1-5)	5 (2-5)	0.664
Bronchoscopy with EBUS†						
Patient cough	4 (1-5)	4 (1-5)	0.389	4 (1-5)	4 (1-4)	0.473
Bronchial secretion	4 (2-5)	4 (2-5)	0.877	4 (2-5)	4 (2-5)	0.425
Feasibility	4 (2-5)	4 (2-5)	0.944	4 (2-5)	4 (2-5)	0.230
Patient movement	5 (2-5)	4 (2-5)	0.814	4 (3-5)	4 (2-5)	0.371
Only EBUS						
Patient cough	—	4 (1-5)	—	5 (4-5)	4 (1-5)	0.800
Bronchial secretion	—	5 (2-5)	—	5 (5-5)	4 (2-5)	0.400
Feasibility	—	5 (3-5)	—	5 (5-5)	4 (3-5)	0.400
Patient movement	—	5 (2-5)	—	5 (5-5)	3 (2-5)	0.400
Patient satisfaction (score)	5 (2-5)	5 (4-5)	0.212	5 (4-5)	5 (4-5)	0.760
PADSS score ≥ 9, 120 min	40 (85)	92 (99)	0.001	45 (98)	47 (100)	0.495
PADSS score 10, 120 min	19 (40)	75 (81)	< 0.0001	30 (65)	45 (96)	0.0002
Time until PADSS 9 (min)	15 (15-60)	15 (15-30)	0.212	15 (15-45)	15 (15-30)	0.574
Time until PADSS 10 (min)	150 (105-180)	45 (15-90)	< 0.0001	60 (45-180)	30 (15-45)	< 0.0001
PSR (total score)	55 (36-77)	55 (41-100)	0.756	56 (43-73)	54 (41-100)	0.959
QoR-23 (total score)	100 (61-112)	101 (60-115)	0.819	102 (60-115)	100 (63-115)	0.846

Part A displays the first comparison between the control group and the 2 PCS groups combined.
In part B, the 2 PCS groups are compared.
Data are presented as median (minimum-maximum), number of patients (%), or median (interquartile range).
*Including TBNA, TBB, and cryotherapy/biopsy.
†Including TBNA/TBB and multistation EBUS in one session.
EBUS indicates endobronchial ultrasound; PADSS, modified Post Anaesthetic Discharge Scoring System; PCS, patient-controlled sedation; PCS-G, patient-controlled sedation with propofol and glycopyrrolate as premedication; PCS-MS, patient-controlled sedation with propofol and morphine-scopolamine as premedication; PSR, Post-Discharge Surgical Recovery scale; QoR-23, Quality of Recovery-23; TBB, transbronchial biopsy; TBNA, transbronchial needle aspiration.

Table 2). The PADSS scores during the 15 to 240-minute postprocedural period (15-min intervals) showed significant differences between the control and PCS groups, favoring the PCS group at all time points (Fig. 2A), and significant differences between the PCS-MS and PCS-G groups, favoring the PCS-G group up to 120 minutes at all time points (Fig. 2B).

The PCS-G group received a significantly higher dose of propofol compared with the PCS-MS group ($P < 0.0001$). The median additional propofol dose administered by the nurse anesthetist in the PCS groups was 35 mg (range, 5 to 300). PCS patients had deeper sedation than controls ($P < 0.0001$); there were no differences in the number of interventions to ensure vital signs among the groups (Table 3). One patient in each PCS group received ephedrine, and 2 patients in the PCS-MS group received atropine (Table 2). Postprocedurally, patients in the control group were more frequently given antagonists against opioids (morphine, alfentanil) and midazolam ($P < 0.0001$; Table 2).

Six adverse events occurred in the control group; one was procedure-related, and the others were related to the drug used for sedation (n = 5). Four patients were confused after sedation and required overnight monitoring; one had epigastric pain. No PCS patient was kept overnight as a result of adverse events from sedation. There were 6 adverse events in the PCS-MS group and 3 in the PCS-G group. In the PCS-MS group, 1 patient reported headache and dizziness, possibly related to the study drug; 1 patient needed unplanned

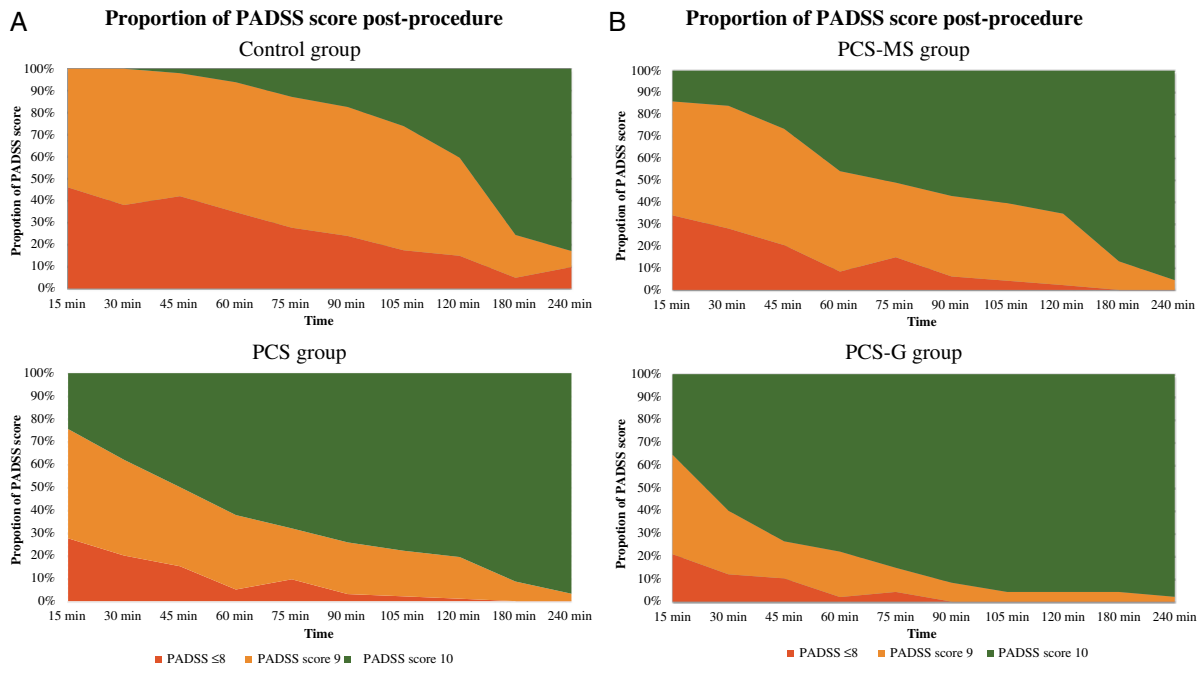

FIGURE 2. A, The proportion of PADSS score postprocedure (15 to 240 min) for the control group and combined PCS groups (PCS-MS and PCS-G). B, The proportion of PADSS score postprocedure (15 to 240 min) for PCS-MS group and PCS-G group. PADSS indicates modified Post Anaesthetic Discharge Scoring System; PCS, patient-controlled sedation; PCS-G, patient-controlled sedation with propofol and glycopyrronium as premedication; PCS-MS, patient-controlled sedation with propofol and morphine-scopolamine as premedication.

overnight admission due to multiple comorbidity; 2 patients developed postprocedural fever; 1 patient reported, directly after administration of premedication, chest pressure, which disappeared after 5 minutes; and 1 patient had a pronounced vasovagal reaction. In the PCS-G group, 1 patient had bronchoscopic findings that resulted in overnight stay; 1 patient felt weak due to ongoing treatment for urinary infection with the need of overnight admission; and 1 patient had a suspected

TABLE 3. Maximum Depth of Sedation, Cardiopulmonary Adverse Events, and Interventions During Procedures to Stabilize Vital Signs or Deepen Sedation

	Control	PCS	*P*	PCS-MS	PCS-G	*P*
Maximum depth of sedation (OAA/S score)	3 (1-4)	2 (1-4)	< 0.0001	2 (1-4)	2 (1-4)	0.150
Bradycardia	0 (0)	0 (0)	—	0 (0)	0 (0)	—
Hypotension	2 (4)	4 (4)	1.000	2 (4)	2 (4)	1.000
Desaturation	4 (8)	11 (11)	0.564	4 (8)*	7 (14)†	0.338
Respiratory depression	4 (8)	8 (8)	1.000	6 (12)	2 (4)	0.140
Semiobstructed/obstructed airway						
Painful stimulation	1 (2)	0 (0)	1.000	0 (0)	0 (0)	—
Jaw thrust (with or without Guedel tube)	0 (0)	7 (7)	0.055	4 (8)‡	3 (6)§	0.695
Assisted ventilation	0 (0)	0 (0)	—	0 (0)	0 (0)	—
NCS in addition to PCS	—	13 (13)	—	8 (16)	5 (10)	0.372

Part A displays the first comparison between the control group and the 2 PCS groups combined.
In part B, the 2 PCS groups are compared.
Data are presented as number of patients (%) or median (minimum-maximum).
*NCS (n = 2).
†NCS (n = 4).
‡NCS (n = 2).
§NCS (n = 1).
NCS indicates nurse-controlled sedation in addition to PCS; OAA/S, Observer's Assessment of Alertness/Sedation scale; PCS, patient-controlled sedation; PCS-G, patient-controlled sedation with propofol and glycopyrrolate as premedication; PCS-MS, patient-controlled sedation with propofol and morphine-scopolamine as premedication.

allergic reaction postprocedurally with unclear origin. The patients' and bronchoscopists' satisfaction scores were high, with no differences among the groups (Table 2).

DISCUSSION

Our results showed that PCS with propofol during FB increased the number of patients ready for discharge in 2 hours compared with NCS with midazolam. Recovery was further shortened when using glycopyrronium instead of morphine-scopolamine despite increased consumption of propofol. Patients and bronchoscopists in all groups experienced high satisfaction concerning ease of procedure.

Bronchoscopy is demanding for anesthesia personnel due to life-threatening risks and limited airway access. According to the British guidelines for bronchoscopy,[1] "conscious" sedation allowing verbal interaction with the patient is desired. With PCS, the patient administers the sedation by activating the PCS set-up, usually by pressing a button. Components such as drugs, doses, infusion rate, and lock-out periods are tailored to each procedure. As the sedation is in the hands of the patient, PCS has an inbuilt barrier against "unconscious" sedation; a deeply sedated patient cannot administer additional doses. PCS has largely been studied in connection with endoscopy during gastrointestinal tract procedures. We have confirmed that sedation with PCS is a promising alternative for FB even without routine opioid addition.

Increasing numbers of complex diagnostic and therapeutic procedures are being performed on an outpatient basis. Avoiding unplanned hospital admission due to sedation side effects or procedure-related complications is in the interest of the patient and the hospital. A rapid postsedation stabilization of vital signs also simplifies surveillance before the patient leaves the hospital. The PCS groups showed better results than the controls with regard to rapid recovery, early patient discharge, and avoidance of hospitalization, with higher PADSS scores for patients using PCS, compared with patients administered midazolam by an NCS at every time point measured between 15 and 240 minutes after the procedure. Recovery time was further shortened by avoiding opioid and scopolamine premedication. Earlier studies have shown that patients receiving propofol demonstrate a faster recovery after bronchoscopy compared with midazolam.[3,5–7] Although the endoscopic team was experienced in managing sedation with midazolam, drug-related confusion causing prolonged recovery and even hospitalization is difficult to anticipate, as adverse events are not necessarily dose-dependent. Antagonists to benzodiazepines and opioids were given when deemed appropriate by the responsible post-procedure clinician to ensure patient safety due to limited postprocedural surveillance. Recovery would most likely have been prolonged and the need for overnight stay greater in the control group if antagonists had not been used.

Airway secretion is often reduced by an antisialagogue to facilitate FB. Scopolamine to reduce airway secretion during FB was standard protocol at our clinic. Compared with glycopyrronium, scopolamine has been shown to more effectively reduce secretion, but it also has a sedative effect,[17] and may affect recovery. Other studies report that anticholinergics do not result in clinically meaningful secretion reduction and can increase patients' HR and blood pressure.[18,19] As we found no differences with regard to airway secretions between scopolamine and glycopyrronium, we now question the need for either during FB.

Successful endoscopic retrograde cholangio pancreatography has been performed with PCS with propofol as the sole agent.[9] Routine use of opioids is probably unnecessary, although opioids may be supplemented during demanding situations, as the addition of alfentanil as a rescue medication has made it possible to complete some FBs that otherwise may have been terminated early. Propofol combined with an opioid improves sedation quality and tolerance to bronchoscopy while reducing coughing,[1,20] but also increases the risk for desaturation.[20] Remifentanil during different procedures including bronchoscopy has been found to provide adequate sedation and analgesia and fast recovery.[21] When used in combination with propofol, however, cautious administration is necessitated due to a significantly increased risk of deep sedation[22] and cardiorespiratory complications.[23] Propofol, which has a narrow therapeutic window, did not result in greater hypoxia or hypotension than midazolam, recapitulating results from previous studies.[3,5–7,20] The PCS technique's safety during FB must be assessed carefully, however, due to a limited number of studies examining PCS during FB thus far. Our study was not powered to assess safety, and we used surrogate outcomes; however, the results from other endoscopic procedures favor PCS over NCS due to reduced risks for desaturation, hypotension,[8] and obstructed airway.[9] Our

PCS groups demonstrated higher frequencies of desaturation and obstructed airway, mostly occurring when rescue propofol was administered by the nurse anesthetist; rescue medication was provided during demanding situations or upon patient difficulties in handling the PCS device, and these modalities made it possible to complete procedures that otherwise might have been terminated early. Appropriate knowledge and experience on the part of the team are necessary both to administer rescue propofol and to manage airway complications to ensure patient safety. The same accounts for another method for sedation by target-controlled infusion.

The patients in the PCS groups reported deeper sedation. We expected that patients' tolerance and bronchoscopists' ease of procedure would be optimal at a sedation level of OAA/S 2. The difference was unexpected but could be explained by a discrepancy in knowledge and experience between the bronchoscopic nurses assessing the control group and nurse anesthetists assessing the PCS groups with regard to sedation estimation.

Strengths and Limitations

The strengths of this trial are the randomized design, a licensed, independent study monitor, and inclusion of advanced protracted procedures and ASA-class III patients. Our design, with three parallel groups, made it possible to compare sedative drugs, sedation methods, and premedication. A fourth arm with NCS and propofol would have made it possible to evaluate the specific effects of PCS. However, earlier findings and experience from our group indicated that PCS is a favorable choice compared with NCS.[9] Obviously, blinding between NCS and PCS to patients and personnel involved in the procedure was not possible. The postprocedural care staff was also not blinded, as the patients had the possibility to carry the information with regard to sedation regime. The primary outcome was protocolled to minimize the influence of subjective assessment, but we cannot exclude the risk of bias; the same also applies to the secondary variables. We found a significant difference in recovery outcomes between the 2 PCS groups, wherein blinding was undertaken by both patients and postprocedure personnel. As the study was conducted at a single center with an experienced pulmonary and anesthesia staff, our results can only be generalized to facilities with similar clinical standards. Moreover, there may be local or national regulations controlling the use of propofol and requiring the presence of anesthesiologists. We found no procedure-specific instruments to assess procedure feasibility and patient satisfaction. A limitation with regard to affected vital signs and serious adverse events also presented due to the limited number of patients.

CONCLUSIONS

We have shown that PCS during bronchoscopy is feasible. Patients using PCS with propofol had shorter recovery compared with NCS with midazolam, without affecting the ease of procedure or patient satisfaction. These results in combination with fewer drug-related adverse events causing unplanned overnight hospital stays support PCS with propofol as a favorable choice for sedation during FB.

REFERENCES

1. Du Rand IA, Blaikley J, Booton R, et al. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. *Thorax*. 2013;68:i1–i44.
2. Wahidi MM, Jain P, Jantz M, et al. American College of Chest Physicians consensus statement on the use of topical anesthesia, analgesia, and sedation during flexible bronchoscopy in adult patients. *Chest*. 2011;140:1342–1350.
3. Clarkson K, Power CK, O'Connell F, et al. A comparative evaluation of propofol and midazolam as sedative agents in fiberoptic bronchoscopy. *Chest*. 1993;104:1029–1031.
4. 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.
5. Crawford M, Pollock J, Anderson K, et al. Comparison of midazolam with propofol for sedation in outpatient bronchoscopy. *Br J Anaesth*. 1993;70:419–422.
6. Stolz D, Kurer G, Meyer A, et al. Propofol versus combined sedation in flexible bronchoscopy: a randomised non-inferiority trial. *Eur Respir J*. 2009;34:1024–1030.
7. Clark G, Licker M, Younossian AB, et al. Titrated sedation with propofol or midazolam for flexible bronchoscopy: a randomised trial. *Eur Respir J*. 2009;34:1277–1283.
8. Lu Y, Hao LX, Chen L, et al. Systematic review and meta-analysis of patient-controlled sedation versus intravenous sedation for colonoscopy. *Int J Clin Exp Med*. 2015;8:19793–19803.
9. Nilsson A, Grossmann B, Kullman E, et al. Sedation during endoscopic retrograde cholangiopancreatography: a randomized controlled study of patient-controlled propofol sedation and that given by a nurse anesthetist. *Scand J Gastroenterol*. 2015;50:1285–1292.
10. Ng JM, Kong CF, Nyam D. Patient-controlled sedation with propofol for colonoscopy. *Gastrointest Endosc*. 2001;54:8–13.
11. Hwang J, Jeon Y, Park HP, et al. Comparison of alfetanil and ketamine in combination with propofol for

patient-controlled sedation during fiberoptic bronchoscopy. *Acta Anaesthesiol Scand*. 2005;49:1334–1338.
12. Smith I, Kranke P, Murat I, et al. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol*. 2011;28: 556–569.
13. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the Observer's Assessment of Alertness/ Sedation Scale: study with intravenous midazolam. *J Clin Psychopharmacol*. 1990;10:244–251.
14. Chung F. Discharge criteria—a new trend. *Can J Anaesth*. 1995;42:1056–1058.
15. Berg K, Idvall E, Nilsson U, et al. Psychometric evaluation of the post-discharge surgical recovery scale. *J Eval Clin Pract*. 2010;16:794–801.
16. Idvall E, Berg K, Unosson M, et al. Assessment of recovery after day surgery using a modified version of quality of recovery-40. *Acta Anaesthesiol Scand*. 2009;53:673–677.
17. Stoelting RK, Hillier SC. Anticholinergic drugs. In: Stoelting RK, Hillier SC, eds. *Handbook of Pharmacology and Physiology in Anesthetic Practice*, 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006: 267–276.
18. Cowl CT, Prakash UB, Kruger BR. The role of anticholinergics in bronchoscopy. A randomized clinical trial. *Chest*. 2000;118:188–192.
19. Malik JA, Gupta D, Agarwal AN, et al. Anticholinergic premedication for flexible bronchoscopy: a randomized, double-blind, placebo-controlled study of atropine and glycopyrrolate. *Chest*. 2009;136:347–354.
20. 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;55:104–109.
21. Kisilewicz M, Rosenberg H, Vaillancourt C. Remifentanil for procedural sedation: a systematic review of the literature. *Emerg Med J*. 2017;34:294–301.
22. Joo JD, In JH, Kim DW, et al. The comparison of sedation quality, side effect and recovery profiles on different dosage of remifentanil patient-controlled sedation during breast biopsy surgery. *Korean J Anesthesiol*. 2012;63:431–435.
23. Cases Viedma E, Andreo García F, Flandes Aldeyturriaga J, et al. Tolerance and safety of 5 models of sedation during endobronchial ultrasound. *Arch Bronconeumol*. 2016;52:5–11.