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Propofol *versus* propofol plus hydrocodone for flexible bronchoscopy: a randomised study

L. Schlatter, E. Pflimlin, B. Fehrke, A. Meyer, M. Tamm and D. Stolz

ABSTRACT: Propofol and the combination of a benzodiazepine and an opiate have been established for sedation in flexible bronchoscopy. It is as yet unknown whether propofol in combination with an opiate is superior to propofol alone to suppress cough during the procedure.

300 consecutive patients undergoing flexible bronchoscopy at a tertiary care university hospital were randomly allocated to receive either the combination propofol and hydrocodone or propofol alone in a double-blind fashion. The primary end-point was the cough score during the procedure as estimated by the physician using a visual analogue scale.

Demographics were similar in both groups. Compared with propofol alone, median (interquartile range) cough scores assessed by physicians, nurses and patients were significantly lower in the group randomised to the combination propofol and hydrocodone (2.5 (1.5–4.0) *versus* 2.0 (1.0–3.0), respectively, $p=0.011$). Additionally, patients receiving the combination required significantly lower doses of propofol than those receiving propofol alone (200 mg (140–280) *versus* 260 mg (180–350), $p<0.0001$). Complex examinations, including bronchoalveolar lavage or transbronchial biopsy, benefited more from additional opiate. The duration of the procedure, time to discharge and complication rate were similar in both groups.

The combination of propofol and hydrocodone is safe and superior to propofol alone for cough suppression in flexible bronchoscopy.

KEYWORDS: Bronchoscopy, cough, intervention, safety, sedation

The current guidelines for bronchoscopy recommend offering sedation to all patients undergoing flexible bronchoscopy, except where there are contraindications [1]. The aim of sedation is to achieve good patient tolerance, comfort and cooperation while reducing complications of the procedure [2–4]. Sedation is associated with high patient satisfaction and willingness to return for a repeat bronchoscopy, if necessary [5]. A survey in the UK has shown that >95% of the centres routinely perform sedated bronchoscopies [6].

Optimal sedation for flexible bronchoscopy has been assessed in a number of studies, which evaluated not only different sedative drug regimens but also particular drug requirements in specific sub-groups of patients [7–10]. In spite of the recommendations of the British Thoracic Society guidelines [1], combined sedation with opiate and a benzodiazepine has been shown to be effective and safe in a randomised, placebo-controlled trial, even in high-risk patients, such as those suffering from chronic obstructive pulmonary disease (COPD) [10]. Recently, propofol (2,6 diisopropylphenol) proved to be an attractive option to combined sedation with midazolam and hydrocodone, particularly if timely discharge is a priority [11–13]. Additionally, propofol seems to provide a higher quality of sedation in terms of neuropsychometric recovery and patient tolerance [14]. There is mounting evidence to suggest that this sedation technique can be safely performed by the non-anaesthesiologist [11, 14].

Propofol is a sedative hypnotic frequently used in the induction and maintenance of anaesthesia [15]. Its pharmacological mechanism is not entirely clear yet, however, it seems to activate the γ-aminobutyric A receptor-chloride ionophore complex [16]. Its rapid onset of action and amnesic properties, coupled with smooth and rapid recovery, make propofol an appealing agent for procedural sedation [11, 17, 18]. The significant

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AFFILIATIONS
Clinic of Pulmonary Medicine and Respiratory Cell Research, University Hospital Basel, Basel, Switzerland.

CORRESPONDENCE
D. Stolz
Clinic of Pulmonary Medicine and Respiratory Cell Research
University Hospital Basel
Petersgraben 4
4031 Basel
Switzerland
E-mail: dstolz@uhbs.ch

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advantage of a faster recovery time compared with other sedatives has been emphasised in several studies [19–22]. However, as yet, there are only limited data evaluating propofol for flexible bronchoscopy and it is as yet unknown whether the combination of propofol and an opiate offers any advantage over propofol alone for sedation during flexible bronchoscopy. Therefore, a prospective, randomised, placebo-controlled, double-blind intervention study was undertaken to determine whether the combination of propofol and hydrocodone is superior to propofol alone to suppress cough during the procedure. The primary end-point was the cough score during the procedure as estimated by the physician using a visual analogue scale (VAS).

METHODS

Patients

300 consecutive patients undergoing elective flexible bronchoscopy from October 2009 to December 2009 were randomly allocated to receive either intravenous propofol or the combination propofol and hydrocodone as a sedative agent (fig. 1). Intubated patients, those receiving an interventional bronchoscopy (*e.g.* laser or stent) and those with known allergy or intolerance to hydrocodone or propofol were not included in the study. Informed consent was obtained from each patient and the study was approved by the Institutional Review Board. The trial was registered with the Current Controlled Trials Database (ISRCTN81533083) (www.controlled-trials.com/isrctn).

Study design

All patients were assessed by a physician and a member of the nursing team trained in anaesthesiology prior to the procedure, including gradation of physical status in accordance with the American Society of Anesthesiologists (ASA) criteria. Bronchoscopies were performed transnasally or transorally with the patients in the semi-recumbent position by a total of five pulmonary fellows under the close supervision of four senior pulmonary physicians. Pulse oximetry was recorded continuously during the procedure and automated noninvasive blood pressure was monitored every 5 min. Supplemental oxygen was offered at 4 $L \cdot min^{-1}$ *via* nasal cannula to all patients. In cases of desaturation $\leqslant$90%, oxygen delivery was increased to 6 $L \cdot min^{-1}$ [23]. Nasal anaesthesia was achieved by applying 2% lidocaine gel nasally. Bronchoscopists were advised to instil 3-mL aliquots of 1% lidocaine over the vocal cords, onto the trachea and both right and left main bronchi. Supplemental local anaesthesia was given as judged by the bronchoscopist. All doses of instilled lidocaine doses were recorded for each patient. No inhaled lidocaine was given prior to the procedure [8]. Patients were given either 4 mg *i.v.* hydrocodone or *i.v.* normal saline as placebo immediately prior to flexible bronchoscopy [10]. Randomisation was performed by arbitrary allocation to one of the two treatment groups based on a computer-generated random list (GraphPad Software, San Diego, CA, USA). Generator and executors of randomisation were separated. Bronchoscopists, nursing team members and patients did not have access to the randomisation code.

Loading doses of propofol were titrated to achieve adequate conscious sedation (onset of ptosis for bronchoscopy). Thereafter, conscious sedation was achieved with an *i.v.* infusion in an intermittent bolus technique. After an initial 10–20 mg *i.v.* propofol, the dose was then carefully titrated

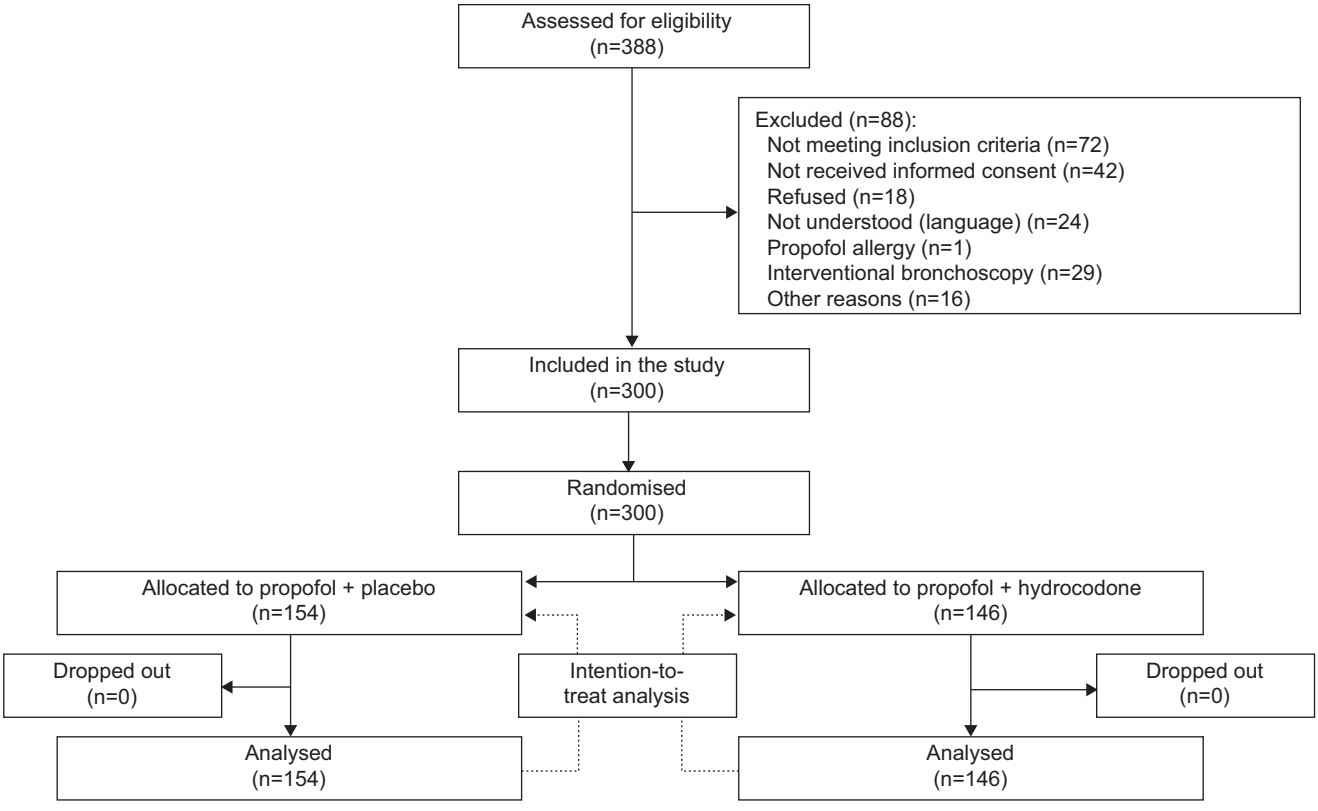

FIGURE 1. Study flow chart for patients included in the study.

according to the ASA physical status classification: for ASA I and II, *i.v.* propofol boluses of 10–20 mg *i.v.* were applied, whereas for ASA III and IV, precisely 10 mg propofol *i.v.* was administered based on the clinical response, as previously described [24]. Between each bolus, a pause lasting $\geqslant$20 s had to be observed. If the effect disappeared during the examination, additional *i.v.* boluses of 10 mg propofol were given, depending on the clinical effect, to maintain the required level of sedation. Signs of pain or discomfort, agitation, persistent cough and inadequate motor or verbal response to manipulation were considered indicators for insufficient sedation, leading to administration of an additional dose of propofol (10–20 mg). The total dose of propofol was documented for each patient.

Diagnostic procedures, *e.g.* brushing, washings, biopsy, bronchoalveolar lavage, endobronchial and transbronchial biopsies, were performed depending on the clinical indication. Haemodynamic parameters, sedation, duration of bronchoscopy, bronchoscopic procedures and complications were noted during the procedure in a standard form specifically designed for the study. Complications were defined as: oxygen desaturation $\leqslant$90%, need for chin support, minor and major bleeding, need for artificial airway or invasive ventilation, need to abort bronchoscopy, need for intensive care unit (ICU)/intermediate care stay, and death.

At the end of the procedure, bronchoscopists and nursing staff charted their perception of cough during the procedure on a 10-cm VAS. Similarly, 2 h after bronchoscopy, patients were also asked to record their perception of cough related to the procedure on a 10-cm VAS. In the scale, 0 denoted no cough and 10 represented incessant cough. Patients were also asked to record discomfort associated with the procedure on a 10 cm VAS. In the scale, 0 denoted no discomfort and 10 represented the greatest possible discomfort. Haemodynamic monitoring was performed immediately before, during and shortly after the procedure (after removal of the bronchoscope), and before transfer from the bronchoscopy suite to the recovery room. Moreover, patient's blood pressure and heart rate were continuously monitored for $\leqslant$2 h after bronchoscopy until discharge. Discharge readiness was evaluated starting at 2 h after the end of the procedure based on subjective (patient's opinion) and objective (orientation to time and place, capability to follow instructions, ability to drink water, ability to stand and walk autonomously, blood pressure, heart rate and oxygen saturation) criteria. In case any of the criteria being not fulfilled, subsequent evaluations were taken every 15–30 min. Additionally, patients were requested to state their perception of cough and of discomfort and to report any side-effects potentially related to the examination 24 h after the procedure.

Data analysis

Assuming a mean cough score of 4.35 in the arm treated with propofol alone and a score of 3.35 in the arm treated with combined sedation, each of them with a standard deviation of 1.5 [11], a total of 286 patients, 143 in each treatment arm, would be needed to achieve a significance level of $p<0.05$ with a power of 0.9. Considering a 5% loss to follow-up, a total of 300 patients were predicted for inclusion. Differences in dichotomous variables were evaluated using the Chi-squared test or Fisher's exact test, as appropriate. Normally distributed parameters were analysed using the unpaired t-test for equality of means. All other continuously non-normally distributed parameters were evaluated using the non-parametric Mann–Whitney U-test or Kruskal–Wallis test, as appropriate. Correlation analyses between physicians and nursing staff VAS were performed using Spearman's rank correlation coefficient. To compare the effect of both sedation regimens in interventions of different complexity levels, patients were dichotomised into two groups: simple procedures (*e.g.* inspection or bronchial washings only) and complex procedures (*e.g.* bronchoalveolar lavage, bronchial brushing, endobronchial biopsy, transbronchial biopsy, transbronchial needle aspiration (TBNA) mediastinum or periphery, or endobronchial ultrasound (EBUS)).

The Statistical Package for Social Sciences programme was used (version 17 for Windows; SSPS Inc., Chicago, IL, USA). All tests were two-tailed; a p-value of <0.05 was considered significant. Results are expressed as mean$\pm$SD or median (interquartile range), unless otherwise stated.

RESULTS

Patient's demographics are presented in table 1. There were no significant differences between both randomised groups in terms of age, presence of comorbidities or ASA physical status.

The indication and the diagnostic procedures in each randomised group are shown in table 2. The main indication for bronchoscopy was pulmonary infection, followed by suspicion of malignancy and bronchial toilette. Accordingly, the most common diagnostic procedures were bronchoalveolar lavage (49%) and bronchial washing (34%). TBNA, both from mediastinum and periphery of the lung, was performed in 18% of the cases. There were no significant differences between both randomised groups concerning indication for bronchoscopy and diagnostic procedures, with exception of the proportion of TBNA.

Compared with propofol alone, the group receiving the combination propofol and hydrocodone showed a significantly lower cough score as estimated by the physician ($p=0.011$), nursing staff ($p=0.031$) and the patient 2 h after the procedure ($p=0.025$), as shown in table 3. In addition, patient's discomfort score 2 h after bronchoscopy was also significantly lower in the group receiving the opiate. The Spearman's rank correlation coefficient of the cough scores was 0.598 ($p<0.0001$) between physician and nurse, 0.165 ($p=0.008$) between physician and patient and 0.273 ($p<0.0001$) between nurse and patient. After 24 h, there were no differences in cough and discomfort scores between the groups.

Compared with propofol alone, the group receiving propofol and hydrocodone required significantly less propofol for sedation during the procedure (260 (180–350) mg *versus* 200 (140–280) mg, $p<0.0001$). The median propofol doses were 3.5 $mg \cdot kg^{-1}$ and 2.8 $mg \cdot kg^{-1}$, respectively ($p<0.0001$). Lidocaine requirements were similar in both groups.

The duration of the examination did not differ significantly in both randomised groups. Nevertheless, there was a trend towards a shorter duration in the group of patients receiving the combination of propofol and hydrocodone (11 (7.8–17) min) compared with propofol alone (14 (9–21) min, $p=0.069$). The time until discharge was similar in both study arms ($p=0.249$).

TABLE 1 Baseline characteristics of 300 consecutive patients undergoing flexible bronchoscopy

Characteristics	Propofol	Propofol + hydrocodone	p-value
Patients n	154	146	
Age yrs	61.8±16.3	64.4±14.0	0.127
Males	89 (58)	72 (49)	0.141
Height cm	170±10	168±9	0.063
Weight kg	71.8±18	69.4±14	0.768
Pack-yrs	23.8±28.8	22.6±27.5	0.933
Comorbidities			
Malignancy	41 (27)	48 (33)	0.219
Stroke	0 (0)	0 (0)	1.000
Diabetes	8 (5)	11 (8)	0.396
Immunosuppression	28 (18)	22 (15)	0.487
Drugs	4 (3)	0 (0)	0.051
Alcoholism	5 (3)	6 (4)	0.682
COPD	27 (18)	22 (15)	0.582
ASA physical status[#] n			
Class I	5	2	0.448
Class II	34	31	0.889
Class III	101	87	0.065
Class IV	0	1	0.488

Data are presented as mean±SD or n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; ASA: American Society of Anesthesiologists. [#]: ASA class was not registered in 14 patients in the propofol group and 25 patients in the combined sedation group.

Haemodynamic findings before, during and after bronchoscopy are shown in table 4. Compared with propofol alone, patients assigned to the combination of propofol and hydrocodone did not show a lower blood pressure at any time during the procedure. The mean lowest oxygen saturation and the mean maximum oxygen requirement during the procedure were also similar across treatment groups.

TABLE 2 Indication for the examination and diagnostic procedures per randomisation group in 300 patients undergoing flexible bronchoscopy

Indication for bronchoscopy	Propofol	Propofol + hydrocodone	p-value
Patients n	154	146	
Infection	44 (28)	38 (26)	0.698
Suspicion of malignancy	35 (22)	30 (20)	0.675
Bronchial toilette	16 (10)	12 (8)	0.556
Pre- or post-interventional bronchoscopy	10 (6)	16 (11)	0.218
Interstitial lung disease	10 (6)	8 (5)	0.810
Cancer follow-up	6 (4)	10 (7)	0.308
Mediastinal lymph nodes/mass	7 (4)	6 (4)	1.000
Chronic cough	2 (1)	7 (4)	0.096
Haemoptysis	5 (3)	3 (2)	0.724
Miscellaneous	19 (12)	16 (11)	0.723
Diagnostic procedures			
Inspection only	24 (16)	32 (22)	0.159
Bronchial washings	55 (35)	46 (31)	0.441
Bronchoalveolar lavage	77 (50)	70 (47)	0.722
Bronchial brushing	20 (12)	16 (10)	0.589
Endobronchial biopsy	27 (17)	23 (15)	0.679
Transbronchial biopsy	23 (14)	16 (10)	0.306
TBNA mediastinum or periphery	35 (23)	19 (13)	0.035
EBUS	2 (1)	0 (0)	0.167

Data are presented as n (%), unless otherwise stated. TBNA: transbronchial needle aspiration; EBUS: endobronchial ultrasound.

TABLE 3 Outcome parameters in patients randomised to sedation with propofol or a combination of propofol and hydrocodone

Characteristics	Propofol	Propofol + hydrocodone	p-value
Patients n	154	146	
Cough score			
Physician VAS	2.5 (1.5–4.0)	2.0 (1.0–3.0)	0.011
Nurse VAS	2.25 (1.0–6.0)	2.0 (1.0–3.6)	0.031
Patient 2 h after bronchoscopy VAS	4.0 (2.0–5.5)	3.0 (1.5–5.3)	0.025
Discomfort score patient 2 h after bronchoscopy VAS	0.5 (0.0–2.0)	0.5 (0.0–1.5)	0.037
Cough score patient 24 h after bronchoscopy VAS	2.0 (1.0–4.5)	2.0 (1.0–4.0)	0.477
Discomfort score patient 24 h after bronchoscopy VAS	1.0 (0.5–2.6)	0.5 (0.0–2.0)	0.138
Propofol dose mg	260 (180–350)	200 (140–280)	<0.0001
Propofol dose mg·kg^{-1}	3.5 (2.6–5.3)	2.8 (2.1–3.9)	<0.0001
Lidocaine dose mg	90 (60–120)	90 (60–120)	0.584
Duration of the bronchoscopy min	14 (9–21)	11 (7.8–17)	0.069
Time until discharge min	120 (99.5–141)	128.5 (109.5–145)	0.249

Data are presented as median (interquartile range), unless otherwise stated. VAS: visual analogue scale.

Table 5 shows the complication rate in both groups. The most common complications were oxygen desaturation ⩽90% (32%) and the need for chin support (31%). The number of patients presenting desaturation ⩽90% on at least one occasion during the procedure was similar in both groups. The number of patients presenting major or minor bleeding, requiring chin support or termination of the procedure did not differ in both randomised groups. Only one patient needed to be transferred to the ICU. There were no deaths. These data are also similar to previous reports [11].

Outcomes in both randomised groups dichotomised by the complexity level of the examination are shown in tables 6 and 7 and figure 2. Patients undergoing simple procedures (*e.g.* inspection or bronchial washings only, n=100) presented similar outcome parameters irrespectively of the applied sedation regimen. In contrast, patients undergoing complex procedures (n=200) showed a significantly lower cough score, lower propofol requirements and a shorter duration of examination if receiving dual sedation with propofol and hydrocodone. There was no difference in lidocaine requirement between both study arms in simple or complex examinations.

Due to the arbitrary imbalance in randomisation for TBNA and EBUS between both treatment groups, we also analysed outcomes of patients undergoing complex procedures excluding those in whom TBNA and/or EBUS were performed. In the subgroup of patients undergoing complex examinations without TNBA/EBUS (n=150), the duration of the procedure was still shorter in the group receiving dual sedation compared with placebo (13 (9–18) min *versus* 14 (9–20.5) min). However, this difference was not anymore statistically significant (p=0.588). In contrast, propofol requirements and cough scores were still statistically significantly lower in the group of patients undergoing complex examinations and receiving hydrocodone in comparison with the group of patients receiving propofol alone (200 (160–270) mg *versus* 260 (200–340) mg, p<0.0001 and 2 (1–3) *versus* 2.5 (1.5–4), p=0.028), even if patients undergoing TBNA and/or EBUS were excluded from the analysis.

TABLE 4 Haemodynamic findings before, during and after bronchoscopy in patients randomised to sedation with propofol or a combination of propofol and hydrocodone

Characteristics	Propofol	Propofol + hydrocodone	p-value
Patients n	154	146	
Initial systolic BP mmHg	128±26	126±28	0.171
Initial diastolic BP mmHg	78±21	75±20	0.113
Final systolic BP mmHg	117±22	116±24	0.325
Final diastolic BP mmHg	67±16	68±16	0.865
2 h re-evaluation			
Systolic BP mmHg	114±21	118±22	0.550
Diastolic BP mmHg	65±15	67±15	0.446
Lowest oxygen saturation %	90.2±5.3	90.4±5.2	0.209
Oxygen requirement L·min^{-1}	5.4±2.8	5.8±2.7	0.262

Data are presented as mean±SD, unless otherwise stated. BP: blood pressure.

TABLE 5 Complications of 300 patients undergoing flexible bronchoscopy randomised to sedation with propofol or a combination of propofol and hydrocodone

Characteristics	Propofol	Propofol + hydrocodone	p-value
Patients n	154	146	
Oxygen desaturation ⩽90%	55 (36)	42 (29)	0.199
Chin support	55 (36)	38 (26)	0.070
Minor bleeding	13 (8)	8 (5)	0.315
Major bleeding	1 (1)	3 (2)	0.289
Termination of the examination	0 (0)	1 (1)	0.304
Intubation	0 (0)	0 (0)	1.000
Intensive care unit	0 (0)	1 (1)	0.304
Death	0 (0)	0 (0)	1.000

Data are presented as n (%), unless otherwise stated.

DISCUSSION

This study has three major findings. First, the combination of propofol and hydrocodone for sedation provides significant benefits for cough suppression in flexible bronchoscopy compared with propofol alone. Second, the peri-interventional complication rate for both sedation regimens is similar. Finally, patients receiving the combination of propofol and hydrocodone required markedly less propofol for providing the same operational conditions than those receiving propofol alone, particularly in those procedures involving more complex examinations. Therefore, there is an additive benefit in combining a pure sedative with an antitussive agent for sedation in flexible bronchoscopy.

To our knowledge, this is the first randomised, double-blind, placebo-controlled study analysing the additional effect of an opiate to propofol for sedation in flexible bronchoscopy. The addition of hydrocodone to propofol lead to a significant cough-suppressing effect, translating into lower cough scores as reported by physicians, nurses and patients. In spite of that, patients' cough and discomfort no longer differed in the two randomised groups 24 h after bronchoscopy. We assume that this is a result of a generally low side-effect rate related to flexible bronchoscopy [25], particularly 1 day after the procedure. Accordingly, the VAS score for cough and discomfort 24 h after the procedure was low for all patients (2.0 (1.0–4.5) and 0.5 (0–2.5), respectively).

The second major finding of this study concerns the complication rate of the procedure. Haemodynamic parameters and procedural complications were similar in both study arms, implying that sedation using the combination of propofol and hydrocodone is as safe as sedation with propofol alone. Indeed, there was a trend to less need for chin support in the patients receiving the combination. Therefore, even if there is concern about more complications, particularly hypoxia, when using combined sedation [1], our data suggest quite the opposite. According to our results, the combination of a sedative with an opiate is as safe as the use of a single sedative. In fact, although propofol sedation by a non-anaesthetist physician is not allowed in several countries, our findings also support the feasibility and safety of propofol sedation even when administered by nurses [26]. Major complications (major bleeding, termination of the examination, intubation, need for ICU or death) were uncommon in both groups. The percentage of 2% was similar to the one described by DANG *et al*. [27] (2.2%) in patients sedated with a benzodiazepine and an opiate.

Besides the decrease in cough scores in the arm receiving propofol plus hydrocodone, we observed a reduction of the propofol doses needed to achieve an adequate degree of sedation using the combined sedation regimen. Taking into account the low cost of hydrocodone, which is the main reason

TABLE 6 Outcome parameters in the subgroup of patients in whom only inspection and/or bronchial washings were performed during flexible bronchoscopy

Characteristics	Propofol	Propofol + hydrocodone	p-value
Patients n	44	56	
Cough score			
Physician VAS	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.951
Nurse VAS	1.5 (0.5–2.0)	1.25 (1.0–3.0)	0.843
Patient 2 h after bronchoscopy VAS	2.0 (1.0–5.0)	2.0 (1.0–4.0)	0.899
Discomfort score patient 2 h after bronchoscopy VAS	0.5 (0.0–1.5)	0.5 (0.0–1.5)	0.992
Propofol dose mg	165 (140–215)	160 (120–220)	0.572
Propofol dose mg·kg^{-1}	2.6 (2.1–3.2)	2.3 (1.8–3.1)	0.150
Lidocaine dose mg	60 (60–90)	90 (60–120)	0.303
Duration of the bronchoscopy min	9 (5–12)	10 (6–15)	0.391

Data are presented as median (interquartile range), unless otherwise stated. VAS: visual analogue scale.

TABLE 7 Outcome parameters in the subgroup of patients in whom bronchoalveolar lavage, bronchial brushing, endobronchial biopsy, transbronchial biopsy, transbronchial needle aspiration and/or endobronchial ultrasound have been performed during flexible bronchoscopy

Characteristics	Propofol	Propofol + hydrocodone	p-value
Patients n	110	90	
Cough score			
Physician VAS	3.0 (2.0–5.0)	2.0 (1.0–3.6)	0.004
Nurse VAS	3.0 (1.4–6.0)	2.0 (1.0–4.0)	0.017
Patient 2 h after bronchoscopy VAS	4.5 (2.5–6.3)	3.0 (1.5–5.5)	0.036
Discomfort score patient 2 h after bronchoscopy VAS	0.5 (0.0–2.0)	0.5 (0.0–1.1)	0.016
Propofol dose mg	300 (220–380)	220 (168–290)	<0.0001
Propofol dose mg·kg^{-1}	4.2 (3.1–5.7)	3.2 (2.4–5.3)	<0.0001
Lidocaine dose mg	90 (60–120)	90 (60–120)	0.292
Duration of the bronchoscopy min	18 (10–26)	14 (9.5–18)	0.020

Data are presented as median (interquartile range), unless otherwise stated. VAS: visual analogue scale.

to favour this compound over other opiates, the combination of propofol and hydrocodone results in net medication cost savings of ~20 Euros per bronchoscopy (corresponding to 60 mg propofol). HOHL *et al*. [19] calculated similar cost savings of 17.33 USD per sedation for procedural sedation in the emergency department. Therefore, routine use of the combination regime would translate to medication savings of >35,000 Euros each year in large respiratory medicine centres, such as our institution, which performs around 2,000 examinations each year. Interestingly, lidocaine doses did not differ among the study arms, either in the overall study group or in the analysis dichotomised by examination complexity. One might hypothesise that bronchoscopists prefer achieving additional sedation and cough suppression by further titrating propofol instead of applying additional lidocaine instillations.

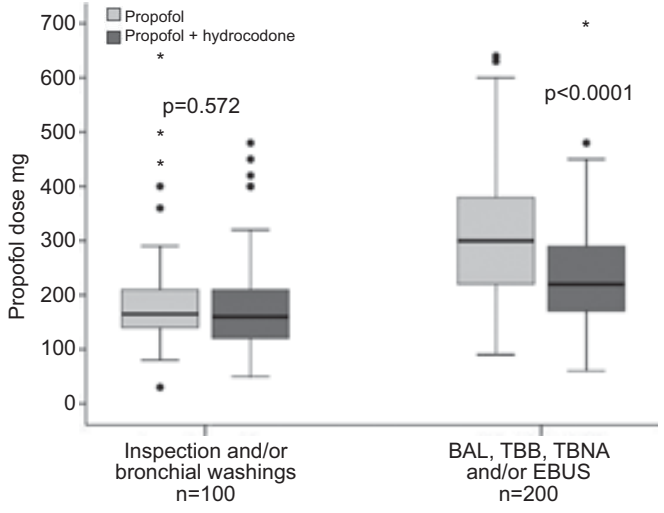

FIGURE 2. Propofol dose, dependent on the sedation regime (propofol *versus* propofol and hydrocodone) in the subgroup of patients undergoing simple bronchoscopic procedures, *e.g.* inspection and/or bronchial washings only, and in the subgroup of patients undergoing complex bronchoscopy procedures, *e.g.* bronchoalveolar lavage (BAL), transbronchial biopsy (TBB), transbronchial needle aspiration (TBNA) and/or endobronchial ultrasound (EBUS). Boxes represent median and interquartile range; whiskers represent range. ●: outliers; *: extreme outliers.

The comparison of outcomes in procedures of different complexity levels revealed a pronounced benefit from the combination of propofol and hydrocodone in patients undergoing complex examinations. In cases in which only inspection or bronchial washings were performed, results from both sedation regimens were similar. In contrast, when complex bronchoscopies were performed, the combination of propofol and hydrocodone resulted in reduced cough and discomfort scores, required propofol doses and, potentially, duration of the procedure. This time-saving effect has been seen as a trend in the overall group and could be more apparent in complex procedures. This is particularly interesting in view of the low cough scores reported in both treatment arms, as one could hypothesise that the reduction in procedure time could be caused by the coughing suppressing effect of hydrocodone. In combination with the fact that propofol allows earlier discharge compared with a regimen including midazolam and hydrocodone [11], the potential additional time-saving during the examination might represent a further argument to support sedation with propofol and hydrocodone, particularly in complex examinations. Similar findings have been recently reported for endoscopic procedures of the gastrointestinal tract. A meta-analysis comparing sedation in gastrointestinal endoscopic procedures found a trend towards a reduction of complications, higher levels of satisfaction and cost-effectiveness for the use of propofol during colonoscopies, and higher levels of patient satisfaction and improved efficacy using propofol during upper gastrointestinal endoscopies, compared with a benzodiazepine-based sedation regime [28].

This study has a few limitations. First, our data is based on well-trained and experienced nursing staff with extensive knowledge in sedation with propofol for all endoscopic procedures, including upper and lower intestinal tract endoscopies. Therefore, our conclusions, particularly on safety, should be put into the local nursing staffs' perspective and should consider the aspects of the pertaining institution, *e.g.* volume of procedures. Second, there was a slightly higher proportion of TBNA in the group receiving propofol alone.

However, it is well known that such imbalances are inherent to the randomisation process and that five out of 100 characteristics of both groups will differ just by chance. Thus, in a study controlling for 33 variables such as ours, a significant difference between the two study arms would be expected statistically for two variables. Moreover, we still observed statistically significant differences in cough scores and propofol requirements in complex examinations between both randomised arms, even after excluding patients undergoing TBNA and/or EBUS from the analysis. Because it is plausible to assume that patients undergoing particularly lengthy examinations, such as TBNA and EBUS, could benefit from additional cough suppression with hydrocodone, we believe that a further study including a larger number of TBNA/EBUS cases would be necessary to definitively confirm whether dual sedation with propofol and hydrocodone is able not only to reduce cough and propofol requirements but also to significantly shorten the duration of the procedure. Strengths of this study are the large number of patients included, the randomised, double-blind and placebo-controlled design, and the diversity of patient comorbidities (*i.e.* COPD) and bronchoscopic procedures.

In conclusion, our data suggest that the combination of propofol and hydrocodone is safe and that its cough-suppressing effect is superior to propofol alone for sedation in patients undergoing flexible bronchoscopy. The significant reduction in propofol requirements when the combination is used leads to an additional cost-saving effect. The higher the complexity of the procedures, the more pronounced are the benefits of the combination, which include a potential shortening of the duration of the procedure. Hence, we suggest, as long as there are no contraindications, the combination of propofol and hydrocodone be adopted as a standard sedation regimen, particularly in patients undergoing complex interventions in flexible bronchoscopy.

SUPPORT STATEMENT

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CLINICAL TRIAL

This trial was registered with the Current Controlled Trials Database (ISRCTN81533083).

STATEMENT OF INTEREST

None declared.

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