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Propofol versus combined sedation in flexible bronchoscopy - a randomized, non-inferiority trial

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Abstract

Combined sedation with a benzodiazepine and an opiate has been proposed as standard sedation for bronchoscopy. Propofol is a sedative-hypnotic with a rapid onset of action and fast recovery time but carries the potential risk of respiratory failure.

Two-hundred consecutive patients were randomly allocated to receive either the combination midazolam and hidrocodone or propofol IV. The primary end-points were the mean lowest saturation during bronchoscopy and the readiness-for-discharge score one hour after the procedure.

The mean lowest oxygen saturation during bronchoscopy did not differ across treatment groups (p=0.422) and the number of patients recording oxygen saturation ≤ 90% on at least one occasion was similar in both groups (p=0.273). The median readiness-for -discharge score one hour after the procedure was significantly higher in the propofol group as compared to the combined sedation group (8 [6-9]) versus 7 [4.75-9], p=0.035). Patient's assigned propofol exhibited less tachycardia during bronchoscopy and for at least one hour after the examination. Minor procedural complications were noted in 71 patients (35.5%) and had a similar incidence in both treatment arms (p=0.460).

Propofol is as effective and safe as combined sedation in patients undergoing flexible bronchoscopy, thus representing an appealing option if timely discharge is a priority.

Introduction

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 whilst reducing complications of the procedure [2-4]. A recent European survey has shown that more than 95% of the centres routinely perform sedated bronchoscopies [5].

Although the ideal sedation for flexible bronchoscopy is not yet defined [1], the combination of a benzodiazepine and an opiate has been shown to improve operating conditions due to it's antitussive effect, to enhance patient's satisfaction and to be safe [6]. Thus, combined sedation using a benzodiazepine and an opiate has been proposed to be adopted as standard sedation for patients without contraindications [7, 8]. Herein, midazolam is the most commonly used benzodiazepine because of its short duration of action [5]. However, pharmacokinetic properties of midazolam include a significant variation in individual dose requirements and a delayed metabolism, leading to accumulation of the drug in about 6 percent of the population [9, 10]. Both attributes may lead to a prolonged recovery period [11-14]. This has important implications for a busy day-case service, including decreased patient throughput, less efficient use of day-care beds, and increased staff-costs.

Propofol (2.6 di-isopropylphenol) is a sedative-hypnotic frequently used in the induction and maintenance of anaesthesia [15]. Its rapid onset of action and amnesic properties, coupled with smooth and rapid recovery, make propofol an appealing agent for procedural sedation [16, 17]. The significant advantage of a faster recovery time as compared to other sedatives has been emphasized in several studies [9, 18-20]. However, as yet, there are only limited data evaluating propofol for flexible bronchoscopy and no safety data comparing propofol with combined sedation in this setting. Therefore, a prospective, randomized, non-inferiority trial was undertaken to determine whether propofol is as effective and safe as combined sedation with a benzodiazepine and an opiate in patients undergoing flexible bronchoscopy. The primary end-points were the mean lowest oxygen saturation during bronchoscopy and the readiness for discharge score one hour after the procedure.

Methods

Patients

Two-hundred consecutive patients undergoing elective flexible bronchoscopy were randomly allocated to receive either intravenous propofol or the combination midazolam and hidrocodone as sedative agent. Intubated patients and those with known allergy or intolerance to midazolam, 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 [21].

Study design

All patients were assessed by a physician and a member of the nursing team trained in anaesthesiology prior to the procedure, which included gradation of physical status in accordance with the American Society of Anaesthesiologists (ASA) criteria and estimation of the Mallampati Score. Bronchoscopies were performed transnasally with the patients in the semi recumbent position by a total of 4 pulmonary fellows under close supervision of 4 pulmonary attendings. Pulse oxymetry was recorded continuously during the procedure and automated non-invasive blood pressure was monitored every 5 minutes. Supplemental oxygen was offered at 4 l/min via nasal cannula to all patients. In case of desaturation ≤ 90%, oxygen delivery was increased to 6l/min [22]. Nasal anaesthesia was achieved by spraying 10% lidocaine in the nasopharynx (4 times) and oropharynx (2 times). Bronchoscopists were advised to instil 3ml aliquots of 1% lidocaine over the vocal cords, onto the trachea and both right and left main bronchi. Instilled lidocaine doses were recorded for each patient. All doses of supplemental local anaesthesia required as judged by the bronchoscopist were recorded for each patient. No inhaled lidocaine was given prior to the procedure [7].

Patients were randomly assigned to either intravenous propofol or the combination of midazolam and hydrocodone. Every patient's assignment

occurred in the waiting room of the bronchoscopy suite by a research nurse. Randomization was through arbitrarily allocation to one of the two treatment groups based on a computer-generated random list (GraphPad Software; San Diego, CA).

Loading doses of propofol and midazolam were titrated to achieve adequate conscious sedation (onset of ptosis for bronchoscopy). Patients assigned the combination of midazolam and hydrocodone received 5 mg intravenous hydrocodone immediately before flexible bronchoscopy.[6] Thereafter, conscious sedation was achieved initially with 2 mg midazolam followed by further 1 to 2 mg intravenous midazolam boluses during the procedure at the endoscopist's discretion.[6] The dose of midazolam during the procedure was titrated to maintain conscious sedation, e.g. induce an altered state of consciousness that minimizes pain and discomfort but still allows a patient to respond to physical stimulation and to maintain an unassisted airway. Patient’s assigned propofol received an intravenous infusion in an intermittent bolus technique: after an initial 20-mg i.v. propofol, the dose was then carefully titrated: for ASA I and II patients, the steps measured 10–20 mg i.v., whereas for ASA III and IV, precisely 10 mg intravenous was administered based on the clinical response, as previously described.[23] Between each bolus, a pause lasting at least 20 s had to be observed. If the effect disappeared during the examination, additional intravenous 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 (10-20mg) or midazolam (1-2mg). The total dose of propofol and midazolam was documented for each patient.

Diagnostic procedures, i.e. brushing, washings, biopsy, bronchoalveolar lavage, endobronchial and transbronchial biopsies, were performed depending on the clinical indication. Hemodynamic parameters, sedation, duration of bronchoscopy, bronchoscopic procedures, and complications were noted during the procedure in a form specifically designed for the study. Complications were defined as: oxygen desaturation ≤ 90%, need for mandible support, minor and major bleeding, arterial hypotension, need for artificial airway or invasive ventilation, need to abort bronchoscopy, need for ICU/intermediate care stay, pneumothorax and death.

At the end of the procedure, bronchoscopists and nursing staff charted their perception of cough during the procedure on a 10 cm visual analogue scale (VAS). Similarly, two hours 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 fear and discomfort associated with the procedure on a 10 cm VAS. In the scale, 0 denoted no fear or discomfort and 10 represented the greatest thinkable fear or discomfort. After one and two hours, respectively, patients were inquired about their readiness for discharge. In the VAS, 0 denoted no readiness for discharge and 10 represented immediate readiness for

discharge. The willingness to repeat flexible bronchoscopy was also documented. Hemodynamic 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 monitored for up to three hours after bronchoscopy until discharge.

Data Analysis

Assuming a mean lowest saturation of 94.8% with a standard deviation of 2.7% in the arm treated with the combination of midazolam and hydrocodone [6], a total of 174 patients, 87 in each treatment arm, would be needed to demonstrate that propofol is associated with a mean lowest saturation within 2% of that of the combination of midazolam and hydrocodone, or better, with 90% power using a one-sided statistical test with an alpha level of 0.05. Assuming a 10% loss of follow-up, a sample size of 200 patients was projected.

The difference in oxygen saturation change between the randomized groups taking into account the initial oxygen saturation was analyzed using a general linear model of repeated measures. Differences in dichotomous variables were evaluated using the Chi-square test or Fischer's Exact test, as appropriate. Normally distributed parameters were analyzed using the Student's 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 rank correlation.

The Statistical Package for Social Sciences (SSPS Inc, version 15 for Windows) program was used. All test were two-tailed; a p value of <0.05 was considered significant. Results are expressed as mean (standard deviation) or median [interquartile range] unless otherwise stated.

Results

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

Table 1. Baseline characteristics of 200 consecutive patients undergoing flexible bronchoscopy

Characteristics	Midazolam + Hydrocodone n = 100	Propofol n = 100	p-value
Age, years (min-max)	61.6 (21-87)	61.0 (23-89)	0.895
Male gender (%)	65 (65%)	62 (62%)	0.659
Height, cm	170.6 (8.6)	171.3 (9.5)	0.853
Weight, kg	76.0 (17.1)	73.9 (16.4)	0.323
Current smoker	28 (28%)	30 (30%)	0.876
Ex-smoker	42 (42%)	41 (41%)	0.886
Pack-years, years	31.1 (33.2)	27.1 (27.1)	0.396
Comorbidities			
Malignancy	35 (35%)	33 (33%)	0.765
COPD	25 (25%)	25 (25%)	1.000
Immunosuppresion	25 (25%)	16 (16%)	0.115
Cardiopathy	20 (20%)	13 (13%)	0.182
Renal failure	4 (4%)	5 (5%)	0.733
Stroke	3 (3%)	3 (%)	1.000
Alcoholism	2 (2%)	3 (3%)	0.651
Platelet counts, $x10^9$ g/l	308 (169)	295 (144)	0.641
ASA physical status	3 [2-3]	3 [2-3]	0.777
Mallampati Score	2 [2-3]	2 [2-3]	0.355

COPD: chronic obstructive pulmonary disease, ASA: American Society of Anesthesiology. Values are expressed as means (standard deviation), medians [interquartile range] or absolute numbers (percentage).

Table 2 shows the indication, number and distribution of diagnostic procedures per patient and randomization group. The main reason for bronchoscopy was pulmonary infection, followed by suspicion of malignancy and interstitial lung

disease. Accordingly, the most common diagnostic procedures were bronchoalveolar lavage (58%) and bronchial washing (33%). Transbronchial needle aspiration, both from mediastinum and periphery of the lung, was performed in 30.5% of the cases. The great majority of patients underwent two (39%) or three (35.5%) diagnostic bronchoscopic procedures. The mean required midazolam dose was 8 mg (3.5) and the mean required propofol dose was 217 mg (131).

Table 2. Indication for the examination, number and distribution of diagnostic procedures per patient and randomization group in 200 patients undergoing flexible bronchoscopy

Indication for bronchoscopy	Midazolam + Hydrocodone n = 100	Propofol n = 100	Total n = 200	p-value
Infection	38 (38%)	28 (28%)	66 (33%)	0.133
Suspicion of malignancy	31 (31%)	31 (31%)	62 (31%)	1.000
Interstitial lung disease	13 (13%)	12 (12%)	25 (12.5%)	0.831
Pre/post interventional bronchoscopy	6 (6%)	7 (7%)	13 (6.5%)	0.774
Hemoptysis	3 (3%)	5 (5%)	8 (4%)	0.721
Chronic cough	2 (2%)	2 (2%)	4 (4%)	1.000
Bronchial toilette	1 (1%)	2 (2%)	3 (1.5%)	1.000
Miscellaneous	6 (6%)	13 (13%)	19 (9.5%)	0.099
Diagnostic procedures				
Bronchial washings	28 (28%)	38 (38%)	66 (33%)	0.133
Bronchial brushing	18 (18%)	13 (13%)	31 (15.5%)	0.329
Endobronchial biopsy	17 (17%)	18 (18%)	35 (17.5%)	0.852
Transbronchial biopsy	24 (24%)	22 (22%)	46 (23%)	0.737
Bronchoalveolar lavage	62 (62%)	54 (54%)	116 (58%)	0.252
TBNA mediastinum	27 (27%)	19 (19%)	46 (23%)	0.179
TBNA periphery	8 (8%)	7 (7%)	15 (7.5%)	0.788
EBUS	3 (3%)	5 (5%)	8 (4%)	0.470
Number of procedures per patient				
Inspection only	4 (4%)	4 (4%)	8 (4%)	1.000
Two	36 (36%)	42 (42%)	78 (39%)	0.469
Three	37 (37%)	34 (34%)	71 (35.5%)	0.383
Four	17 (17%)	15 (15%)	32 (16%)	0.705
Five	4 (4%)	4 (4%)	8 (4%)	1.000
Six	2 (2%)	1 (1%)	3 (1.5%)	1.000

TBNA: transbronchial needle aspiration; EBUS: endobronchial ultrasound. Values are expressed as absolute numbers (percentage).

Primary end-points

Mean lowest oxygen saturation during the procedure

The mean lowest oxygen saturation during the procedure was similar across treatment groups (p=0.422, Figure 1). Correspondingly, there was no significant difference in the oxygen saturation change from baseline through re-evaluation between patients randomized to the combination of midazolam and hydrocodone and those randomized to propofol (Figure 2, p=0.644). The number of patients who recorded a saturation ≤ 90% on at least one occasion was also similar in both groups (25 midazolam/hydrocone versus 32 propofol, p=0.273). The median maximum oxygen requirement during the procedure did not differ in patients treated with midazolam and hydrocodone (4 litres [4-8]) and in those treated with propofol (4 litres [4-8], p=0.081).

Readiness for discharge score one hour after the procedure

The median readiness-for-discharge score one hour after the procedure was 7 [4.75-9] in patients sedated with the combination of midazolam and hydrocodone and 8 [6-9] in patients sedated with propofol (p=0.035). One hour after the procedure, a readiness for discharge score ≥ 6 was noted in 59 patients treated with the combination midazolam and hydrocodone and in 75 patients treated with propofol (p=0.003). A total of 17 patients was unable to answer any question at the re-evaluation one hour after the procedure (16 midazolam/hydrocodone versus 1 propofol, p<0.001). Eight patients were still drowsy and unable to speak at two hours after the procedure (7 midazolam/hydrocodone versus 1 propofol, p=0.030).

Secondary End-points

Hemodynamic findings before, during and after bronchoscopy are shown in Table 3.

Table 3. Hemodynamic findings before, during and after bronchoscopy in patients randomized to sedation with the combination of midazolam and hydrocodone (n=100) and propofol (n=100)

Characteristics	**Midazolam + Hydrocodone n = 100**	**Propofol n = 100**	**p-value**
Baseline systolic BP, mmHg	138 (22)	134 (24)	0.105
Baseline diastolic BP, mmHg	79 (17)	80 (15)	0.713
Baseline heart rate, bpm	83 (14)	83 (16)	0.816
Initial systolic BP, mmHg	133 (26)	128 (23)	0.060
Initial diastolic BP, mmHg	80 (16)	78 (16)	0.192
Initial heart rate, bpm	88 (15)	83 (15)	**0.040**
Final systolic BP, mmHg	135 (24)	125 (26)	**0.002**
Final diastolic BP, mmHg	78 (15)	73 (23)	0.098
Final heart rate, bpm	91 (16)	87 (15)	**0.013**
1 h Reevaluation systolic BP, mmHg	122 (20)	122 (22)	0.832
1 h Reevaluation diastolic BP, mmHg	71 (14)	71 (17)	0.993
1 h Reevaluation heart rate, bpm	90 (14)	85 (17)	**0.040**
2 h Reevaluation systolic BP, mmHg	131 (20)	129 (18)	0.906
2 h Reevaluation diastolic BP, mmHg	78 (11)	76 (11)	0.288
2 h Reevaluation heart rate, bpm	84 (13)	83 (14)	0.469

Values are expressed as means (standard deviation), medians [interquartile range] or absolute numbers (percentage). BP: blood pressure; bpm: beat per minute; min: minutes; mmHg: millimeter mercury.

As compared to combined sedation with midazolam and hydrocodone, patient's assigned propofol exhibited less tachycardia during bronchoscopy and this difference in heart rate was statistically significant for at least one hour after the procedure. Systolic blood pressure was higher at the end of bronchoscopy in patients sedated with the combination midazolam and hydrocodone (p=0.002).

Procedural complications were noted in 71 patients (35.5%) and had a similar incidence in both treatment arms (p=0.460, Figure 3). The most common complications were the need for chin support (n=68, 34%) and oxygen saturation ≤ 90% (n=57, 28.5%). A nasopharyngeal tube was required in three cases; one patient was transferred to the ICU. There were no deaths.

The median duration of the procedure was similar in patients receiving midazolam and hydrocodone (17 minutes [10-24]) and in those receiving propofol (17 minutes [9-28], p=0.941, Table 4). There was also no difference in the required dose of lidocaine in both randomized groups (p=0.926). Cough scores, as judged by the bronchoscopists and nursing staff, did not differ in patients randomized to combined sedation or propofol. Conversely, cough scores, as judged by patients' themselves, were significantly lower in the group treated with combined sedation as compared to propofol. There was no difference in the discomfort related to the procedure across treatment groups (p=0.162).

Arterial carbon dioxide was assessed in 42 of the 50 patients (84%) with chronic obstructive pulmonary disease before the procedure. In these patients, mean FEV_1 was 1.54 ± 0.67 liters and 56 ± 19 % predicted. Mean pCO_2 was 40.2 ± 4.9 mmHg. Hypercapnic status, as defined by $pCO_2 \geq 45$ mmHg in the arterial blood gas analysis, was evidenced in 5 cases. In hypercapnic patients, chin support was required in three cases and oxygen saturation ≤ 90% was documented in 2 cases during the procedure. These figures did not differ significantly from the ones observed in normocapnic patients (p=0.716 and p=0.891, respectively).

Table 4. Outcome parameters in patients randomized to sedation with the combination of midazolam and hydrocodone (n=100) and propofol (n=100)

Characteristics	**Midazolam + Hydrocodone n = 100**	**Propofol n = 100**	**p-value**
Duration of the procedure, min	17 [10-24]	17 [9-28]	0.941
Lidocaine dose, mg	132 (40)	136 (44)	0.926
Cough score physician, VAS	4 [2 -6.25]	4.5 [2-6.75]	0.781
Cough score nurse, VAS	4.25 [2-7]	5 [3-7]	0.489
Cough score patient, VAS	0 [0-3]	2 [0-6]	**<0.001**
Discomfort score patient, VAS	0 [0-0]	0 [0-0]	0.162
Fear from today's bronchoscopy, VAS	0 [0-2]	0 [0-3]	0.151
Fear from future bronchoscopy, VAS	0 [0-0]	0 [0-0]	**<0.007**
Readiness for discharge after 1 hour, VAS	7 [4.75-9]	8 [6-9]	**0.035**
Readiness for discharge after 2 hours, VAS	8.5 [7-10]	9 [7.25-10]	0.131

Values are expressed as means (standard deviation) or medians [interquartile range]. VAS: visual analogue scale.

Discussion

This study demonstrates that the mean lowest oxygen saturation and the number of procedural complications are similar in patients receiving the combination midazolam and hidrocodone or propofol for sedation during flexible bronchoscopy. Herein, operating conditions, as assessed by duration of the procedure or need for supplemental lidocaine were also comparable. Therefore, propofol is a valid alternative to combined sedation with a benzodiazepine and an opiate. The use of propofol was associated with a significantly higher readiness-for-discharge score one hour after the examination and a lower proportion of persistent sedation two hours after bronchoscopy whereas the use of combined sedation was associated with lower cough scores as assessed by patients. Hence, both drugs regimens have peculiar sedating characteristics and the choice of one over the other might rely on the preferences of the patient and bronchoscopist as well as on infrastructural circumstances, i.e. expected time to discharge.

To the authors' knowledge this is the first randomized, controlled, non-inferiority trial comparing propofol with the combination of a short-acting benzodiazepine and an opiate as a sedative agent during flexible bronchoscopy. The combination of a short acting benzodiazepine and an opiate has been shown to improve operating conditions due to its antitussive effects and to improve patient satisfaction. Thus, combined sedation has been suggested to be adopted as

standard sedation for patients without contraindications, particularly if diagnostic bronchoscopic procedures, e.g. transbronchial biopsy, are performed [6, 7]. Former studies on propofol were performed utilizing a benzodiazepine alone or a long acting benzodiazepine [24-26]. Randell et al. showed a significantly lower respiratory frequency in patients receiving the combination diazepam and fentanyl as compared to propofol alone [26]. However, midazolam has replaced diazepam in most centres due to its shorter duration of action compared to diazepam and is now by far the most common sedative used during bronchoscopy [1, 5].

Crawford et al. compared sedation for flexible bronchoscopy provided by incremental doses of midazolam alone with that provided by a computer-controlled infusion of propofol [25]. Operator and patient acceptability, anxiolysis, and the effect on systolic arterial pressure did not differ between the groups. Conversely, oxygen saturation during the procedure fell more in those who received propofol than in those who received midazolam (83% in the propofol group and 86% in the midazolam group). It is well known that both propofol and midazolam may produce respiratory depression [25, 27]. Contrary to the current British Thoracic Society recommendations, oxygen supplementation was not routinely provided in that study. Supplemental oxygen is routinely given to all patients undergoing flexible bronchoscopy at most institutions [1, 28]. Our randomized trial showed that if supplemental oxygen is routinely provided during bronchoscopy, propofol does not cause a greater fall in oxygen saturation than the combination of midazolam and hydrocodone.

Kestin et al. examined the cardiovascular stability and rate of recovery in patients receiving propofol infusions with or without alfentanyl for rigid oesophagoscopy and (or) bronchoscopy [24]. All patients received a neuromuscular blocker during induction of anaesthesia and were intubated for the endoscopic procedure. The authors found no difference in hemodynamic parameters; recovery time or adverse events in both groups but patients receiving propofol combined with alfentanil required a mean lower dose of propofol during the procedure. Because all patients where intubated for the examination, this study does not allow any inferences about safety in non-intubated patients undergoing routine flexible bronchoscopy. Nevertheless, it is tempting to speculate that the combination of propofol and hydrocodone could reduce the total propofol doses required during flexible bronchoscopy.

Although both drugs performed equally in regard to safety in this study, we found significant differences between the two groups in the post operational VAS readiness-for-discharge score and the number of patients presenting signs of persistent sedation two hours after the procedure. These findings are in accordance with previous data suggesting that midazolam causes a significant impairment of memory and motor reactions 60 minutes after the end of the procedure [9, 25]. Accordingly, central nervous system impairment may persist for at least 3.5 hours after antagonism of midazolam sedation with flumazenil, although patients may have a subjective feeling of alertness, which might have dangerous consequences [29].

Considering the mean doses required in our study, sedation with propofol were five times more expensive than sedation with the combination of midazolam and hydrocodone (mean costs 15.66 ± 9.46 € versus 2.92 ± 0.18 €, respectively). Nevertheless, costs related to sedative medication represent only a small percentage of the overall cost of the bronchoscopy. Although figures may vary markedly across countries, continuous peri-interventional monitoring generates up to one third of the procedure cost in Switzerland. Prolonged sedation may prevent discharge, thus disrupting a tight schedule and increasing procedural costs. Therefore, having proving that propofol is as effective and safe as standard combined sedation with a benzodiazepine and an opiate, these data suggest that propofol might be an appealing option if timely discharge is a priority either for the patient or medical staff.

Interestingly, cough scores, as judged by patients' themselves, were significantly lower in the group treated with combined sedation as compared to propofol. In contrast, cough scores judged by the bronchoscopists and nursing staff did not differ between randomized groups. We hypothesize that these findings can be explained by the amnesic effect of midazolam. According to several previous studies, wake up time for combined sedation with an opiate and benzodiazepine is 35–60 minutes and discharge time 75–120 minutes after the procedure [30-32]. Alternatively, propofol might have a shorter or less potent effect on the cough reflex as compared to the combination of midazolam and hydrocodone [33, 34].

The incidence of adverse events is our study was similar to that described in previous reports [9, 35]. Noteworthy, it is now appreciated that oxygen desaturation during invasive endoscopic procedures in a common phenomenon, both with [9, 35] and without oxygen supplementation [31]. This observation emphasizes the importance of standard pulse oxymetry and oxygen supplementation during flexible bronchoscopy, as stated in the British Thoracic Society Guidelines [1]. Additionally, particular care should be taken in patients at higher risk of carbon dioxide retention during bronchoscopy [1]. Preoperative arterial blood gas assessment is usually required in such patients. Although our data do not demonstrate an obviously increased risk of propofol sedation in hypercapnic patients, monitoring of transcutaneous carbon dioxide may be useful to avoid the complications related to any kind of sedation in these high risk patients [36].

This study has a few limitations. We used a standardized VAS score, a subjective tool, to assess readiness for discharge after bronchoscopy. Taking into account that the short half-life of propofol is well described [9], we believe that it was fair to apply a clinical tool for appraising discharge suitability. Thus, we refrained from performing formal measurements of motor and verbal function. Further, this was not a blinded study and the specific macroscopic characteristics of propofol facilitate its identification. In this context, concerns regarding potential drops in oxygen saturation might have caused "less than optimal" dose in those patients allocated to the propofol arm. This might be the reason why patients treated with propofol had higher cough scores (judged by patients themselves).

Another factor to consider is that nursing staff in our hospital has considerable expertise in sedation with propofol for all endoscopic procedures, including upper and lower intestinal tract endoscopies. Therefore, and similarly to many other European countries, there is no requirement for an anaesthesiologist to be present during sedation in our institution. Hence, caution might be needed when introducing this sedative regimen in other institutions with less experience nursing staff. Strengths of this study are the large number of patients included, the diversity of bronchoscopic procedures and the original randomized, non-inferiority design.

In conclusion, our data suggest that propofol is as effective and safe as combined sedation in patients undergoing flexible bronchoscopy. Therefore, propofol represents a valid alternative to combined sedation with a benzodiazepine and an opiate, particularly if timely discharge is a priority.

Competing interests

None of the authors declare any conflict of interests

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1. British Thoracic Society guidelines on diagnostic flexible bronchoscopy. *Thorax* 2001: 56 (Suppl 1): i1-21.
2. Gonzalez R, De-La-Rosa-Ramirez I, Maldonado-Hernandez A, Dominguez-Cherit G. Should patients undergoing a bronchoscopy be sedated? *Acta Anaesthesiol Scand* 2003: 47(4): 411-415.
3. Putinati S, Ballerin L, Corbetta L, Trevisani L, Potena A. Patient satisfaction with conscious sedation for bronchoscopy. *Chest* 1999: 115(5): 1437-1440.
4. Matot I, Kramer MR. Sedation in outpatient bronchoscopy. *Respir Med* 2000: 94(12): 1145-1153.
5. Pickles J, Jeffrey M, Datta A, Jeffrey AA. Is preparation for bronchoscopy optimal? *Eur Respir J* 2003: 22(2): 203-206.
6. Stolz D, Chhajed PN, Leuppi JD, Brutsche M, Pflimlin E, Tamm M. Cough suppression during flexible bronchoscopy using combined sedation with midazolam and hydrocodone: a randomised, double blind, placebo controlled trial. *Thorax* 2004: 59(9): 773-776.
7. Stolz D, Chhajed PN, Leuppi J, Pflimlin E, Tamm M. Nebulized lidocaine for flexible bronchoscopy: a randomized, double-blind, placebo-controlled trial. *Chest* 2005: 128(3): 1756-1760.
8. Stolz D, Pollak V, Chhajed PN, Gysin C, Pflimlin E, Tamm M. A randomized, placebo-controlled trial of bronchodilators for bronchoscopy in patients with COPD. *Chest* 2007: 131(3): 765-772.
9. Clarkson K, Power CK, O'Connell F, Pathmakanthan S, Burke CM. A comparative evaluation of propofol and midazolam as sedative agents in fiberoptic bronchoscopy. *Chest* 1993: 104(4): 1029-1031.
10. Shelley MP, Wilson P, Norman J. Sedation for fibreoptic bronchoscopy. *Thorax* 1989: 44(10): 769-775.
11. Williams TJ, Bowie PE. Midazolam sedation to produce complete amnesia for bronchoscopy: 2 years' experience at a district general hospital. *Respiratory medicine* 1999: 93(5): 361-365.

12. Williams TJ, Nicoulet I, Coleman E, McAlaney C. Safety and patient acceptability of intravenous midazolam for fibre optic bronchoscopy. *Respiratory medicine* 1994: 88(4): 305-307.
13. Chudnofsky CR, Weber JE, Stoyanoff PJ, Colone PD, Wilkerson MD, Hallinen DL, Jaggi FM, Boczar ME, Perry MA. A combination of midazolam and ketamine for procedural sedation and analgesia in adult emergency department patients. *Acad Emerg Med* 2000: 7(3): 228-235.
14. Bailey PL, Pace NL, Ashburn MA, Moll JW, East KA, Stanley TH. Frequent hypoxemia and apnea after sedation with midazolam and fentanyl. *Anesthesiology* 1990: 73(5): 826-830.
15. Bryson HM, Fulton BR, Faulds D. Propofol. An update of its use in anaesthesia and conscious sedation. *Drugs* 1995: 50(3): 513-559.
16. Zed PJ, Abu-Laban RB, Chan WW, Harrison DW. Efficacy, safety and patient satisfaction of propofol for procedural sedation and analgesia in the emergency department: a prospective study. *Cjem* 2007: 9(6): 421-427.
17. Berkenbosch JW, Graff GR, Stark JM, Ner Z, Tobias JD. Use of a remifentanil-propofol mixture for pediatric flexible fiberoptic bronchoscopy sedation. *Paediatric anaesthesia* 2004: 14(11): 941-946.
18. Hohl CM, Nosyk B, Sadatsafavi M, Anis AH. A cost-effectiveness analysis of propofol versus midazolam for procedural sedation in the emergency department. *Acad Emerg Med* 2008: 15(1): 32-39.
19. Rodrigo MR, Jonsson E. Conscious sedation with propofol. *British dental journal* 1989: 166(3): 75-80.
20. Gasparovic S, Rustemovic N, Opacic M, Premuzic M, Korusic A, Bozikov J, Bates T. Clinical analysis of propofol deep sedation for 1,104 patients undergoing gastrointestinal endoscopic procedures: a three year prospective study. *World J Gastroenterol* 2006: 12(2): 327-330.
21. http://www.controlled-trials.com/isrctn/trial/. [cited; Available from:
22. Chhajed PN, Glanville AR. Management of hypoxemia during flexible bronchoscopy. *Clin Chest Med* 2003: 24(3): 511-516.
23. Heuss LT, Schnieper P, Drewe J, Pflimlin E, Beglinger C. Safety of propofol for conscious sedation during endoscopic procedures in high-risk

patients-a prospective, controlled study. *The American journal of gastroenterology* 2003: 98(8): 1751-1757.
24. Kestin IG, Chapman JM, Coates MB. Alfentanil used to supplement propofol infusions for oesophagoscopy and bronchoscopy. *Anaesthesia* 1989: 44(12): 994-996.
25. Crawford M, Pollock J, Anderson K, Glavin RJ, MacIntyre D, Vernon D. Comparison of midazolam with propofol for sedation in outpatient bronchoscopy. *British journal of anaesthesia* 1993: 70(4): 419-422.
26. Randell T. Sedation for bronchofiberoscopy: comparison between propofol infusion and intravenous boluses of fentanyl and diazepam. *Acta anaesthesiologica Scandinavica* 1992: 36(3): 221-225.
27. Bell GD, Reeve PA, Moshiri M, Morden A, Coady T, Stapleton PJ, Logan RF. Intravenous midazolam: a study of the degree of oxygen desaturation occurring during upper gastrointestinal endoscopy. *British journal of clinical pharmacology* 1987: 23(6): 703-708.
28. Smyth CM, Stead RJ. Survey of flexible fibreoptic bronchoscopy in the United Kingdom. *Eur Respir J* 2002: 19(3): 458-463.
29. Andrews PJ, Wright DJ, Lamont MC. Flumazenil in the outpatient. A study following midazolam as sedation for upper gastrointestinal endoscopy. *Anaesthesia* 1990: 45(6): 445-448.
30. Greig JH, Cooper SM, Kasimbazi HJ, Monie RD, Fennerty AG, Watson B. Sedation for fibre optic bronchoscopy. *Respiratory medicine* 1995: 89(1): 53-56.
31. Webb AR, Doherty JF, Chester MR, Cummin AR, Woodhead MA, Nanson EM, Flack ST, Millard FJ. Sedation for fibreoptic bronchoscopy: comparison of alfentanil with papaveretum and diazepam. *Respiratory medicine* 1989: 83(3): 213-217.
32. Bright E, Roseveare C, Dalgleish D, Kimble J, Elliott J, Shepherd H. Patient-controlled sedation for colonoscopy: a randomized trial comparing patient-controlled administration of propofol and alfentanil with physician-administered midazolam and pethidine. *Endoscopy* 2003: 35(8): 683-687.

33. Guglielminotti J, Rackelboom T, Tesniere A, Panhard X, Mentre F, Bonay M, Mantz J, Desmonts JM. Assessment of the cough reflex after propofol anaesthesia for colonoscopy. *British journal of anaesthesia* 2005: 95(3): 406-409.
34. Eddy NB, Halbach H, Braenden OJ. Synthetic substances with morphine-like effect: clinical experience; potency, side-effects, addiction liability. *Bulletin of the World Health Organization* 1957: 17(4-5): 569-863.
35. Schnapp LM, Cohen NH. Pulse oximetry. Uses and abuses. *Chest* 1990: 98(5): 1244-1250.
36. Evans EN, Ganeshalingam K, Ebden P. Changes in oxygen saturation and transcutaneous carbon dioxide and oxygen levels in patients undergoing fibreoptic bronchoscopy. *Respiratory medicine* 1998: 92(5): 739-742.

Figure legends:

Figure 1. Mean lowest oxygen saturation during bronchoscopy was 93.2% (5.9) in patients assigned the combination of midazolam and hydrocodone and 91.8% (6.9) in patients assigned propofol, p=0.422.

Figure 1

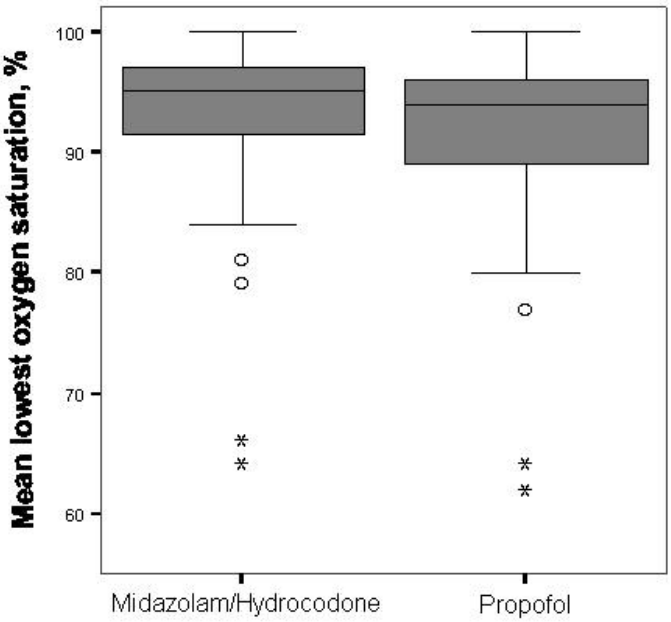


Figure 2. Mean oxygen saturation at baseline (midazolam/hydrocodone 96.5% (4) vs. propofol 96.3% (3.9), p=0.625); at the beginning of the procedure (95.8% (5.9) vs. 96.6% (2.9), p=0.436); at the end of the procedure (95.8% (3.4) vs. 95.7% (3.8), p=0.653) and at one hour reevaluation (94.0% (3.3) vs. 93.5% (5.5), p=0.481, respectively). There was no significant different in the oxygen saturation change during time across groups (p=0.644).

Figure 2

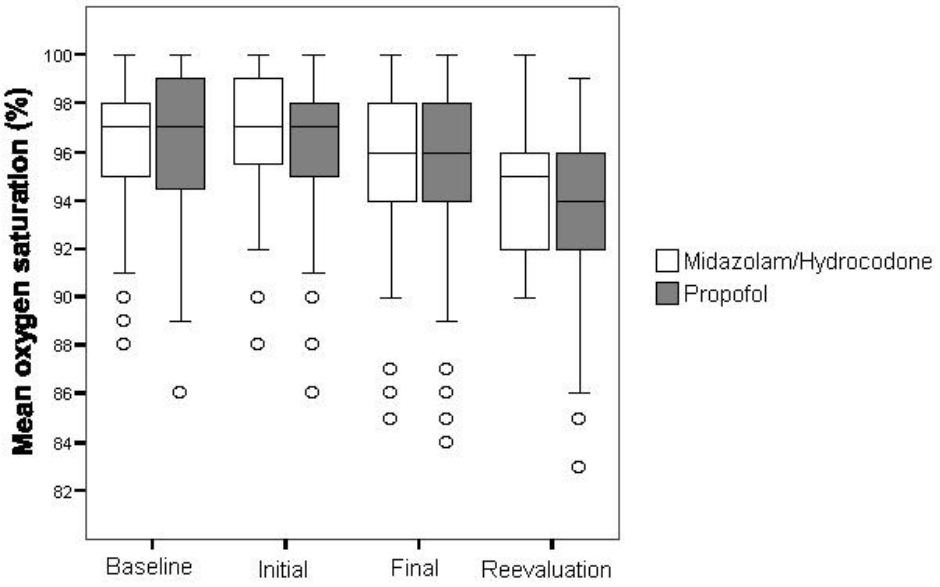
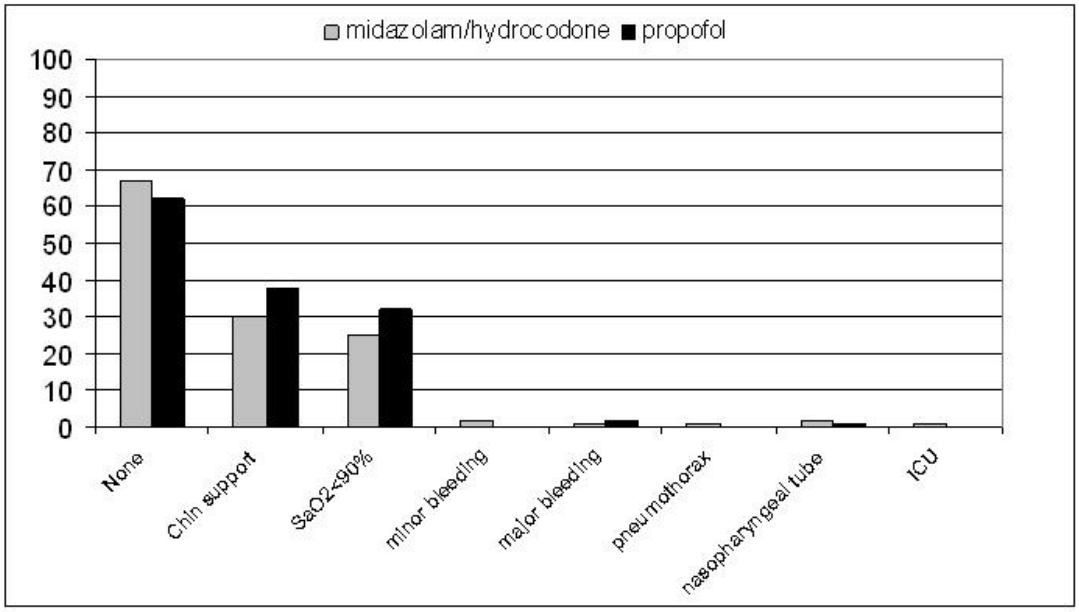


Figure 3. Complications of bronchoscopy in patients assigned the combination midazolan and hydrocodone (n=100) and propofol (n=100).

Figure 3


midazolam/hydrocodone
propofol
100
90
80
70
60
50
40
30
20
10
0
None
Chin support
SaO2<90%
minor bleeding
major bleeding
pneumothorax
nasopharyngeal tube
ICU