Sedation during Flexible Bronchoscopy in Patients with Pre-Existing Respiratory Failure: Midazolam versus Midazolam plus Alfentanil

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For editorial comment see p. 276

Key Words

Alfentanil · Bronchoscopy · Conscious sedation · Midazolam · Respiratory insufficiency · Transcutaneous blood gas monitoring

Abstract

Background: The use of sedation during flexible bronchoscopy (FB) is undisputed; however, the combination of benzodiazepines and opiates, although reasonable, is suggested to cause hypoventilation, particularly in patients with pre-existing respiratory failure. **Objectives:** To assess respiratory function during FB. **Methods:** Transcutaneous PCO₂ (PtCCO₂), oxygen saturation, patients' tolerance, time after FB until recovery and application of drug dosage were assessed in patients receiving either midazolam with alfentanil (n = 15) or midazolam alone (n = 15) for sedation for FB. **Results:** There were no differences in PtCCO₂ values during FB between the two groups (all p > 0.05). However, PtCCO₂ significantly increased over time in both groups (both p < 0.001; RM-ANOVA on ranks). Minimum oxygen saturation (SaO₂) [89 (interquartile range 79.8/92.8) vs. 86 (interquartile range 82.3/87.8)%; p = 0.46] and the duration until recovery, i.e., achieving an ALDRETE score of ≥ 9 [30 (interquartile range 10/90) vs. 10 (interquartile range 10/105) min; p = 0.68] were comparable for monosedation and combined sedation, re-

spectively. The total amount of midazolam [4.0 (interquartile range 4.0/4.0) vs. 2.0 (interquartile range 2.0/2.0) mg; p < 0.001] was lower in patients receiving combined sedation. Significantly lower scores for pain and asphyxia, and a clear tendency to less nausea and cough were reported by patients receiving combined sedation. **Conclusions:** Combined sedation during FB produced a comparable degree of desaturation and hypoventilation, and is associated with a comparable time to full recovery compared to monosedation in patients with pre-existing respiratory failure. Importantly, FB using combined sedation is better tolerated by patients despite only 50% midazolam consumption.

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Introduction

Flexible bronchoscopy (FB) is a well-established tool used in the diagnosis and management of a variety of diseases affecting the airways and lungs [1, 2]. In addition to local anaesthesia, patients are often sedated for

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this procedure in order to facilitate the examination and promote comfort [3–5]. While the British Thoracic Society (BTS) guidelines recommend patient sedation without mentioning any contraindications [1], there is a lack of data in actual support of this recommendation [1, 6].

The short-acting benzodiazepine midazolam is most often used in combination with different opiates for sedation given the sedative and amnestic properties of benzodiazepines, and the analgesic and antitussive properties of opiates [1, 7–9] although newer drugs like fospropofol have also been introduced for FB [9, 10]. However, sedation induced by the combination of drugs is supposedly associated with a greater extent of deoxygenation and carbon dioxide (CO₂) retention, particularly in patients with pre-existing respiratory failure [1]. For this reason, current BTS guidelines do not recommend the routine use of a benzodiazepine in conjunction with an opiate during FB in patients with respiratory failure [1]. Importantly, no studies on sedation practices have been performed in the specific group of patients with pre-existing respiratory failure undergoing FB. Therefore, the current study aimed to assess respiratory function during FB in patients with pre-existing respiratory failure, specifically targeting deoxygenation and CO₂ retention. Differences between sedation with a combination of midazolam and alfentanil, compared to sedation with midazolam alone, have been specifically addressed.

Methods

The study protocol was approved by the Institutional Review Board for Human Studies at Albert Ludwigs University, Freiburg, Germany, and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Written informed consent was obtained from all patients.

Patients

Hospitalized patients with pre-existing stable respiratory failure requiring FB were consecutively enrolled in the study. Respiratory failure was defined as PaO₂ <60 mm Hg and/or PaCO₂ >45 mm Hg following arterial blood gas (ABG) analysis during room air breathing. Exclusion criteria were <50.000 thrombocytes/ μ l, an International Normalized Ratio >2.5, respiratory acidosis (pH <7.35), systolic blood pressure <90 mm Hg or catecholamine treatment. Treatment with unfractionated or low molecular-weight heparin was stopped at least 12 h prior to FB.

Sedation and FB

All FBs were performed by one experienced investigator (W.W.), in accordance with international guidelines [1]. Local anaesthesia (nebulized and liquid oxybuprocaine) of the upper air-

way tract (including transnasal application) and endobronchial local anaesthetics were administered to all patients. The first 15 consecutive patients received 2 mg of midazolam (M group), intravenously, exactly 3 min prior to FB. The following 15 consecutive patients also received 2 mg of midazolam 3 min prior to FB; additionally, however, these patients received 0.5 mg of alfentanil intravenously (MA group). If necessary, additional boluses of intravenous midazolam were administered to all patients during FB, at the discretion of the endoscopist, and according to international guidelines [1].

Questionnaires

As recommended [4], the investigator and the entire cohort of patients assessed the Global Tolerance Score by means of a visual-analogue scale (0 = no bother, 100 = intolerable), as well as 5 specific sensations: nausea, ease of introduction, asphyxia, cough and pain (0 = nonexistent; 100 = unbearable). The Tolerance Score is defined as the arithmetic mean of global tolerance and the mean of the 5 above-mentioned specific sensations [4]. The American Society of Anesthesiologists' (ASA) score was used to assess patients' physical status [11]. The ALDRETE score (global assessment of post-anaesthetic condition) was used to assess patients' recovery after bronchoscopy [12].

Study Design (fig. 1)

For baseline measurements, ABG were taken from the arterialized earlobes of all patients while they were breathing room air (NPT7, Radiometer, Copenhagen, Denmark). Within 24 h prior to FB, lung function parameters (Masterlab-Compact Labor®, Jaeger, Hochberg, Germany) were assessed in all patients using body plethysmography. For transcutaneous PCO₂ (PtcCO₂) monitoring (TCM40 Monitoring System Tina®, Radiometer) a sensor was placed on the left anterior chest wall [13]. PtcCO₂ monitoring, oxygen saturation (SaO₂), and heart rate were continuously monitored from 1 h prior to FB to 2 h following FB. Supplemental oxygen was adjusted before and during FB in order to achieve an SaO₂ >90%. The flow rate of oxygen was recorded throughout the entire protocol. ABG measurements were made at the following time points: (1) immediately prior to FB, (2) 2 h after FB, (3) during the night after FB (at 01:00 AM), and (4) 24 h after completion of FB. During the protocol, the time point, the number of midazolam boluses, the start/end time of FB and the beginning of each of the different interventions (transbronchial biopsy and/or bronchiolo-alveolar lavage) were recorded. At 10, 20, 30, 60, 90 and 120 min t_{10, 20, 30, 60, 90, 120}) after FB, the following parameters were recorded: ALDRETE score, PtcCO₂ measurements and amount of supplemental oxygen delivered. The need for further monitoring (heart rate, blood pressure, SaO₂, PtcCO₂) was assessed 2 h after termination of FB, and was defined by the following criteria: increased amount of oxygen supply compared to pre-intervention conditions, pH <7.35, Δ PaCO₂ >10 mm Hg compared with pre-intervention values or an ALDRETE score <9. If further observation and monitoring were necessary, re-assessment of the above-listed criteria was performed every subsequent hour until further observation was no longer needed. At the very end of the observation period, patients assessed their Global Tolerance Score. All post-interventional complications occurring within 24 h after the intervention were recorded.

Fig. 1. Study design.

Predetermination of Study Endpoints

Since sedation is known to cause significant hypoventilation in patients with respiratory failure, reduced alveolar ventilation, as estimated from $PtccO_2$, was chosen as the primary endpoint. Here, the difference of peak $PtccO_2$ during FB between the M group and MA group served as the primary endpoint. Secondary endpoints were defined as follows: (1) the need for prolonged monitoring (yes vs. no); (2) patients' Tolerance Score, and (3) the time until the ALDRETE score was ≥ 9 (min). In addition, the following details were also recorded: amounts of oxybuprocaine (ml) and midazolam (mg); ABG following FB (PaO_2 and $PaCO_2$, mm Hg); mean rise in $PtccO_2$ compared to baseline (mm Hg); minimum SaO_2 (%) during FB, and post-intervention complications.

Statistical Analysis

Statistical analysis was performed using Sigma-Stat® (version 3.1, Systat Software, Inc., Point Richmond Calif., USA). Unless

otherwise stated, all data are presented as mean $\pm$ standard deviation (SD) after testing for normal distribution (Kolmogorov-Smirnov test). The null hypothesis (H_0) was defined as there being no difference in peak $PtccO_2$ between the two intervention groups. Sample size determination (unpaired t-test, power 0.9, two-sided type I error 0.05) was performed with an estimated SD of 6 mm Hg for the mean difference of $PtccO_2$, and a difference of at least 10 mm Hg [14] between the two intervention groups. Accordingly, at least 9 subjects were needed in each group for H_0 rejection. The target sample size of 15 patients in each group was in order to increase the power of the analysis. A two-group comparison was performed using the unpaired t-test for normally distributed data. The paired t-test was used for the quantitative measurements. For nonnormally distributed data, the Wilcoxon signed rank test was used. Furthermore, one-way repeated measures analysis of variance (RM-ANOVA), including an all-pairwise comparison (normally/nonnormally distributed data:

Fig. 2. Change in PtCO₂ during and after FB in the M group (n = 15) and in the MA group (n = 15). T bars represent 95% CI.

Fig. 3. Change in SaO₂ during and after FB in the M group (n = 15) and in the MA group (n = 15). T bars represent 95% CI. *p < 0.05

Table 1. Demographic data, lung function parameters and blood gases measured during room air breathing of patients of the M group (n = 15) and patients of the MA group (n = 15)

	M Group	MA Group	95% CI	p value
Male/female, n	10/5	12/3		0.7
Age, years	63.4 ± 11.9	58.7 ± 15.5	-15.1/ 5.6	0.4
ASA score (III/IV)	6/9	7/8		1.0
Pre-existing hypercapnia, n	7	7		
BMI	23.4	24.5	NF	0.5
FVC, %pred.	46	52	NF	0.06
FEV ₁ , %pred.	35 ± 18	40 ± 26	-12/22	0.5
FEV ₁ /VC _{max} %pred.	57 ± 20	48 ± 15	-23/4	0.2
PaCO ₂ , mm Hg	41.2 ± 6.8	45.7 ± 8.0	-1.6/10.7	0.1
PaO ₂ , mm Hg	55.0	48.0	NF	0.007
pH	7.43 ± 0.03	7.42 ± 0.04	-0.03/-0.02	0.6
HCO ₃ ⁻ , mmol/l	26.4 ± 3.4	28.4 ± 3.3	0.8/4.8	0.1

%pred = %predicted; BMI = body-mass index; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity; NF = normality test failed; PaCO₂ = arterial partial pressure of carbon dioxide; PaO₂ = arterial partial pressure of oxygen; TLC = total lung capacity.

Table 2. Underlying diseases and type of intervention during FB in patients of the M group (n = 15) and patients of the MA group (n = 15)

	M Group	MA Group
<i>Underlying disease</i>		
COPD	5	7
Interstitial lung disease	3	1
Pneumonia	2	0
Lung carcinoma	0	3
Unclassified myopathy	1	0
Marginal zone B cell lymphoma	1	0
CREST syndrome	1	0
Pulmonary siderosis	1	0
Microscopic polyangiitis	1	0
Chronic thromboembolic pulmonary hypertension	0	1
Pulmonary arterial hypertension	0	2
Cystic fibrosis	0	1
<i>Diagnostic interventions</i>		
Broncho-alveolar lavage	10	10
Transbronchial biopsy	6	3
Endobronchial biopsy	3	2
Bronchial brushing	2	4

COPD = Chronic obstructive pulmonary disease;

Holm-Sidak/Tukey test), was used for comparing different time points during and after FB. The Fisher exact test and the χ^2 were used for categorical data. For normally distributed data, the 95% confidence interval of the mean (95% CI) is given where appropriate. Statistical significance was assumed with a p value <0.05 .

Results

A total of 30 patients (M group: $n = 15$; MA group: $n = 15$) were investigated (table 1). The only difference between the two groups was that of baseline PaO_2 during spontaneous breathing (table 1). Duration of FB was 18.8 ± 8.5 min in the M group versus 18.5 ± 9.0 min in the MA group ($p = 0.85$). The underlying diseases as well as the interventions performed during FB are summarized in table 2.

PtcCO₂ Monitoring

Although PtcCO_2 values during FB did not differ between the two groups (all $p > 0.05$), PtcCO_2 changed significantly over time in both groups (both $p < 0.001$; RM-ANOVA on ranks; fig. 2). In the M group, PtcCO_2 was higher at 120 min after FB compared to PtcCO_2 at the start of FB (49.5 ± 10.0 vs. 45.5 ± 8.2 ; $\Delta -4.0 \pm 4.0$; 95% CI $-6.2/-1.8$; $p = 0.002$); however, PtcCO_2 remained unchanged in the MA group (45.2 ± 10.6 vs. 43.1 ± 9.2 ; $\Delta -2.1 \pm 4.6$; 95% CI $-4.7/0.4$; $p = 0.09$). Regardless of the sedation method, there was no difference in PtcCO_2 increase during FB, when comparing patients with pre-existing hypercapnia ($n = 14$) to normocapnic patients ($n = 16$), i.e. $\Delta 11.9 \pm 4.6$ vs. $\Delta 9.6 \pm 4.4$ mm Hg; $p = 0.16$).

Oxygenation and Heart Rate

There was no group difference in minimum SaO_2 during FB [M group: 89 (interquartile range 79.8/92.8) vs. MA group: 86 (interquartile range 82.3/87.8)%; $p = 0.46$], nor did any of the patients from either group desaturate below 80% of SaO_2 during FB (fig. 3). However, SaO_2 before and after FB was higher in the M compared to the MA group (fig. 3). The median amount of supplemental oxygen supply did not differ between the M and MA groups at the start [3 (interquartile range 2.0/5.8) vs. 4 (interquartile range 2.0/5.8) l/min; $p = 0.55$] or at the end of FB [6 (interquartile range 2.3/8.8) vs. 8 (interquartile range 5.3/9.8) l/min; $p = 0.25$]. However, oxygen supply increased during FB from 3 (interquartile range 2.0/5.8) to 6 (interquartile range 2.3/8.8) l/min ($p = 0.02$) in the M group as well as in the MA group from 4.3 ± 2.6 to

7.8 ± 3.8 l/min ($\Delta -3.5 \pm 3.0$; 95% CI 1.8/5.1; $p < 0.001$) with no difference in the mean increase in oxygen supply [0.0 (interquartile range 0.0/4.0) vs. 4.0 (interquartile range 0.0/5.0); $p = 0.34$].

Heart rate increased during FB in both groups (both $p < 0.001$); however, there were no differences in heart rate during FB between the two groups (all $p > 0.05$).

Arterial Blood Gases

Baseline PaO_2 was higher in the M than in the MA group (table 1). In addition, 2 h after FB, PaO_2 was higher in the M than in the MA group (68.5 ± 11.1 vs. 60.9 ± 8.2 mm Hg; $\Delta 7.7$; 95% CI $-15/-0.4$; $p = 0.039$). However, ABG at night and at 24 h following FB did not differ between the two groups (all $p > 0.05$).

Medication

There was a difference in the total amount of midazolam administered between the M [4.0 (interquartile range 4.0/4.0)] and the MA groups [2.0 (interquartile range 2.0/2.0) mg; $p < 0.001$]; the total amount of local anaesthesia (oxybuprocaine) did not differ between the M and MA groups (20 ± 5 vs. 19 ± 6 ml; $\Delta 1.1$; 95%CI $-5/-3$; $p = 0.58$).

Recovery

With the exception of t_{20} [8 (interquartile range 7.0/9.0) vs. 9 (interquartile range 8.0/9.0); $p = 0.044$], the M and MA groups did not differ in the ALDRETE score at any of the assessed time points following FB (all $p > 0.05$). Furthermore, there was no group difference in the mean time span required to reach an ALDRETE score of ≥ 9 [M group: 30 (interquartile range 10/90) vs. MA group: 10 (interquartile range 10/105) min; $p = 0.68$]. However, 7 patients required 120 min to achieve an ALDRETE score of 9 after completion of FB (3 in the M group and 4 in the MA group).

Questionnaires and Complications

Tolerance Scores and the assessment of specific sensations by both patients and the investigator are shown in figures 4 and 5. While 1 patient in the MA group developed a pneumothorax after transbronchial biopsy, no further serious complications were seen in either group. Prolonged monitoring (1 h) was required for 1 patient only (MA group).

Fig. 4. Patients' Tolerance Scores, Global Tolerance Scores and ratings of the specific sensations associated with FB. Values assessed by means of a visual-analogue scale (0 = no bother, 100 = intolerable); n = 15 in each group. 'Tolerance Score' = arithmetic mean of global tolerance and the mean of the 5 specific sensations.

Discussion

The major finding of the present study was that despite pre-existing respiratory failure, neither peak $PtCO_2$, $PtcCO_2$ increase, nor oxygenation during FB differed when sedation was induced with a combination of alfentanil and midazolam compared to sedation with midazolam alone. However, the combination of midazolam and alfentanil was associated with less discomfort to the patient. For this reason, the present study favours the combination of midazolam and alfentanil for sedation during FB in patients with pre-existing respiratory failure.

The present study also demonstrates that alveolar hypoventilation, as estimated from an increase in $PtcCO_2$, is substantial during FB when sedation is administered in patients with respiratory failure. However, there was no differential effect of sedation with midazolam versus sedation with the combination of midazolam and alfentanil on hypoventilation, as estimated from the primary endpoint, peak $PtcCO_2$. Furthermore, the increase in $PtcCO_2$ in patients with respiratory failure was also similar to

Fig. 5. Investigator's Tolerance Scores, Global Tolerance Scores and ratings of the specific sensations associated with FB. Values assessed by means of a visual-analogue scale (0 = no bother, 100 = intolerable); n = 15 in each group. 'Tolerance Score' = arithmetic mean of global tolerance and the mean of the 5 specific sensations.

that in former studies including those investigating patients without respiratory failure [14, 15]. Therefore, there is increasing evidence that pre-existing respiratory failure does not aggravate the hypoventilation caused by sedation for FB.

While hypoxemia was observed during FB in the present study, it occurred to a similar degree in both groups investigated although those who received combined sedation had significantly lower baseline PaO_2 and SaO_2 compared to those receiving monosedation. Furthermore, SaO_2 after FB was slightly higher in the midazolam group. However, no severe desaturation was observed during FB in either group. This is in line with previous findings including those of patients not suffering exclusively from respiratory failure [16]. Nevertheless, the present study has shown that oxygen supply during FB needs to be significantly increased in both groups without any differences in the increase in oxygen supply in order to prevent oxygen desaturation.

In the present study, FB was better tolerated when the combination of midazolam and alfentanil was used, com-

pared to sedation with midazolam alone. In particular, subjectively reported pain and asphyxia were significantly lower when using the combined sedation, with a clear trend towards less nausea and cough. In addition, the investigator (although not blinded) also rated the FB to be more tolerable with the use of combined sedation. It is also worth noting that the total amount of midazolam administered was twofold higher when midazolam alone was given. As pointed out above, the degrees of hypoventilation and desaturation were comparable and, in addition, the time to fully recover from sedation was not different between the two groups. Nevertheless, 120 min after FB, PtcCO₂ remained elevated only in the M group, but not in the MA group. Therefore, the better tolerance, the similar changes on oxygen supplementation and in PtcCO₂, and the lower dose of midazolam associated with the combined sedation clearly favours the use of midazolam in combination with alfentanil for FB in patients with pre-existing respiratory failure.

According to BTS guidelines, monitoring via oximetry during FB is recommended in all patients whereas monitoring of PtcCO₂ is suggested to be most useful in patients at higher risk of CO₂ retention [1]. However, this recommendation only refers to the time period during the intervention. The present study provides evidence that further PtcCO₂ monitoring, in addition to oximetry in patients with pre-existing respiratory failure, is also useful since hypercapnia only resolves slowly, and, in the majority of patients, full recovery (as estimated from the ALDRETE score) is reached within 120 min of completion of FB. Finally, subgroup analysis revealed that the increase in PaCO₂ was comparable in hypercapnic and non-hypercapnic patients. This observation clearly challenges previous observations, where higher baseline PtcCO₂ values were found to increase the risk of developing a higher peak PtcCO₂ [14].

This study has several limitations which need to be addressed: firstly, randomization of the type of sedation

and blinding of both the patients and the investigator was not performed. However, it is unlikely that this has affected the primary endpoint of the present study, namely, peak PtcCO₂ during FB. Nevertheless, future studies are needed to confirm the findings of the present study in a randomized, double-blinded setting. Secondly, the findings of the present study are only valid for the use of alfentanil. Therefore, generalization of the findings to other opiates is supposed to be limited. Thirdly, data about the effects of the drugs used on blood pressure are lacking since blood pressure was not assessed during FB in the present study.

In conclusion, compared to the use of midazolam alone, combined sedation with midazolam and alfentanil used for FB in patients with pre-existing respiratory failure produces a similar degree of desaturation and hypoventilation lasting 2 h after FB, as estimated from extended continuous oximetry and PtcCO₂ monitoring. Furthermore, combined sedation is associated with a comparable time required to reach full recovery when compared to monosedation with midazolam, but FB using combined sedation is better tolerated despite only 50% midazolam consumption.

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Conflict of Interest

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