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Original Article / Özgün Makale

Comparison of midazolam and midazolam-fentanyl combination for sedation in convex probe endobronchial ultrasound

Konveks prob endobronşiyal ultrasonda sedasyon için midazolam ve midazolam-fentanil kombinasyonunun karşılaştırılması

Sevda Şener Cömert, Benan Çağlayan, Ali Fidan, Banu Salepci, Elif Torun Parmaksız

Department of Chest Diseases, Dr. Lütfi Kırdar Kartal Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Background: This study aims to investigate the sedative effects, possible side-effects, and impact on patient and bronchoscopist satisfaction of midazolam and midazolam-fentanyl combination in patients undergoing convex probe endobronchial ultrasound (CP-EBUS).

Methods: Between May 1, 2011 and June 18, 2011, 50 consecutive patients (35 males, 15 females; mean age 51.6±14.6 years; range 17 to 79 years) admitted to our clinic for CP-EBUS for mediastinal or hilar staging or histological diagnosis were included in this prospective study. All patients underwent topical anesthesia with lidocaine. The patients were divided into two groups in the order of admittance. 2 mg of midazolam + 0.5 μ/kg with increasing doses of fentanyl was applied to the first 25 of the patients (group F) and 2 mg starting dose with increasing doses of midazolam was applied to the second 25 of the patients (group M). Before and after the procedure and during the procedure, oxygen saturation and hemodynamic variables of the patients, total duration of the procedure, and duration of procedure per aspirated lymph node and per aspiration were recorded. At the end of the procedure, amnesia level, satisfaction levels of the patients and bronchoscopist, repeatability of the procedure, cough, pain, and dyspnea were evaluated. The satisfaction level of the bronchoscopist during the procedure and sedation or procedure-related complications were also noted.

Results: During the procedure, cough symptoms were significantly lower in group F than the group M ($p<0.05$). The patient and bronchoscopist satisfaction levels were significantly higher in the group F ($p=0.007$, $p<0.001$). The duration of the procedure per aspirated lymph node was significantly lower in F group ($p<0.05$). Minimum and maximum heart rate during and at the end of the procedure were significantly lower in group F compared to the group M ($p<0.05$). No significant difference in the level of amnesia was found between the two groups.

Conclusion: The combination of fentanyl and midazolam shortens the duration of procedure and increases the patient and physician satisfaction compared to the use of midazolam alone without any significant difference in the rate of complications.

Keywords: Endobronchial; fentanyl; midazolam; sedation; ultrasonography.

ÖZ

Amaç: Bu çalışmada konveks prob endobronşiyal ultrason (CP-EBUS) yapılan hastalarda midazolam ile midazolam-fentanil kombinasyonunun sedatif etkileri, olası yan etkileri ve hasta ve bronkoskopi uzmanının memnuniyeti üzerine etkileri araştırıldı.

Çalışma planı: Bu prospektif çalışmaya 1 Mayıs 2011 - 18 Haziran 2011 tarihleri arasında mediastinal veya hiler evreleme veya histolojik tanı amacı ile CP-EBUS yapılmak üzere kliniğimize başvuran ardışık 50 hasta (35 erkek, 15 kadın; ort. yaş 51.6±14.6 yıl; dağılım 17-79 yıl) dahil edildi. Tüm hastalara lidokain ile topikal anestezi uygulandı. Hastalar başvuru sırasına göre iki gruba ayrıldı. İlk 25 hastaya (grup F) 2 mg midazolam + 0.5 μ/kg ile artan dozda fentanil uygulandı ve ikinci 25 hastaya (grup M) 2 mg'den başlayıp artan dozda midazolam uygulandı. İşlem öncesi ve sonrası ve işlem sırasında hastaların oksijen satürasyonu ve hemodinamik parametreleri, işlemin toplam süresi ve lenf bezi başına ve aspirasyon başına düşen işlem süresi kayıt edildi. İşlem sonunda, amnezi düzeyi, hastaların ve bronkoskopi uzmanının memnuniyet düzeyi, işlemin tekrarlanabilirliği, öksürük, ağrı ve nefes darlığı değerlendirildi. Bronkoskopistin işlem sırasındaki memnuniyet düzeyi ve sedasyona veya işleme bağlı gelişen komplikasyonlar da kayıt edildi.

Bulgular: İşlem sırasında öksürük semptomları M grubuna kıyasla, F grubunda anlamlı düzeyde daha düşük idi ($p<0.05$). Hasta ve bronkoskopi uzmanının memnuniyet düzeyi, F grubunda anlamlı düzeyde daha yüksek idi ($p=0.007$, $p<0.001$). Aspire edilen lenf bezi başına düşen işlem süresi, F grubunda anlamlı düzeyde düşük idi ($p<0.05$). İşlem sırasında ve işlem sonunda ölçülen minimum ve maksimum kalp hızı, M grubuna kıyasla, F grubunda anlamlı derecede daha düşük idi ($p<0.05$). Amnezi düzeyi açısından iki grup arasında anlamlı bir fark bulunmadı.

Sonuç: Fentanil ve midazolam kombinasyonu, komplikasyon oranında anlamlı bir fark olmaksızın, midazolamın tek başına kullanılmasına kıyasla, işlem süresini kısaltmakta ve hasta ve hekim memnuniyetini artırmaktadır.

Anahtar sözcükler: Endobronşiyal; fentanil; midazolam; sedasyon, ultrasonografi.

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Correspondence: Sevda Şener Cömert, M.D. Dr. Lütfi Kırdar Kartal Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, 34865 Cevizli, İstanbul, Turkey.
Tel: +90 532 - 361 26 08 e-mail: sevdasenercomert@gmail.com

Convex probe endobronchial ultrasound (CP-EBUS)-guided transbronchial needle aspiration (TBNA) is a novel, minimally invasive, bronchoscopic technique used in the evaluation of intrathoracic lymph nodes, mediastinal lesions, and regional nodal staging of lung cancer. Diagnostic accuracy of CP-EBUS-guided TBNA is high and it is an alternative method to mediastinoscopy.[1] Most of the published original reports described the introduction of the dedicated CP-EBUS into the airway under general anesthesia.[1,2] Considering the cost saving of CU-EBUS under conscious sedation compared to general anesthesia, many pulmonologists prefer performing CP-EBUS in an outpatient setting. However, appropriate patient sedation during CP-EBUS is essential for the satisfaction of the patient and the bronchoscopist at the time of the procedure.

Sedative medications decrease bronchoscopy-related anxiety, oropharyngeal irritation, cough, chest discomfort, and dyspnea, thus increasing the tolerability of the CP-EBUS.[3] There is little standardization in the choice of sedative agents. The American College of Chest Physicians recommends the use of a combination of benzodiazepines and opiates.[4] Benzodiazepins are the most frequently used sedative agents thanks to their ease of administration, rapid action, and availability of an antidote.[3,5,6] They also offer prolonged sedation and cognitive impairment.[3,7-9] Midazolam, a short-acting benzodiazepine with anxiolytic, amnestic, and hypnotic effects, is used during bronchoscopy to achieve conscious sedation.[10] Midazolam is a selective substrate of CYP3A4 and CYP3A5, causing variability in metabolic activity and numerous drug-drug interactions.[3,11,12] Fentanyl is a rapid-onset and short-acting opioid which has analgesic and cough suppression properties. Combining these two medications offers synergistic effects and attenuates sympathetic tone during the CP-EBUS.[10,13]

The CP-EBUS-guided TBNA has a relatively low tolerability and longer duration of process than conventional bronchoscopy.[1,14] The insertion via the mouth rather than a nostril is necessary due to the size of the CP-EBUS instrument; however, oral introduction of bronchoscope has been associated with lower patient satisfaction.[1,14] When sampling from more than one lymph node station is necessary, particularly in patients with lung cancer for mediastinal staging, the duration of process becomes longer. The efficacy of sedation is of utmost importance during CP-EBUS.

In this study, we aimed to investigate the sedative effects, possible side-effects, and impact on patient and bronchoscopist satisfaction of midazolam and midazolam-fentanyl combination in patients undergoing CP-EBUS.

PATIENTS AND METHODS

This is a prospective, single center study where patients received midazolam or midazolam-fentanyl combination for sedation during CP-EBUS. The study protocol was approved by the local ethics committee and an informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Helsinki Declaration.

Fifty consecutive patients (35 males, 15 females; mean age 51.6±14.6 years; range 17 to 79 years) who underwent CP-EBUS between May 1, 2011 and June 18, 2011 at the bronchoscopy unit of the Pulmonary Department of a tertiary referral hospital for diagnostic or staging purposes were included. The CP-EBUS was requested by the treating clinician in patients with suspected malignant diseases, tuberculosis, sarcoidosis or in patients with a known malignant disease for disease staging. Inclusion criteria were as follows: >16 years of age, the presence of CP-EBUS indication, and normal liver function test, blood urea and creatinine levels. Patients with hemodynamic instability (heart rate <60 bpm or >120 bpm or systolic blood pressure <90 mmHg or >180 mmHg) were excluded. Exclusion criteria were as follows: unwilling to sign an informed consent, the presence of an uncontrolled coagulopathy (platelets <20,000/mm^3, INR >1.3), or a known hypersensitivity to benzodiazapines or fentanyl.

Procedure and protocol

The heart rate and blood pressure were measured and oxygen saturation and heart rate were monitored. Before starting CP-EBUS, 10% lidocaine was applied topically as a local anesthetic to the rhinopharyngeal and oropharyngeal region. During the CP-EBUS, all patients received supplementary oxygen which was administered using an oxygen delivery system at a flow rate of 2 L/min. The patients were divided in two groups in the order of admittance. Two milligrams of midazolam + 0.5 μ/kg with increasing doses of fentanyl was applied to the first 25 of the patients (group F) and 2 mg starting dose with increasing doses of midazolam (group M) was applied to the second 25 of the patients. Sedation was administered by a single anesthesiologist. The patients were evaluated for sedation with the Ramsey scale by the anesthetist. The CP-EBUS was performed by a single bronchoscopist in supine position and by the oral route in all patients. One milliliter, 2% lidocain solution was applied at the vocal cords, after entering the trachea, at the right and left main bronchi. After passing the vocal cords and

entering the trachea, the time period of processing was initiated and ended by exiting the trachea, and the total time period was recorded. Before, after, and during the procedure, heart rate and oxygen saturation were recorded, while before and after the procedure, blood pressure was recorded. The total duration of the procedure, the duration of procedure per aspirated lymph node and per aspiration were also recorded and calculated. Duration of the procedure per aspirated lymph node was calculated by dividing the total duration of the procedure by the number of aspirated lymph nodes, whereas duration of the procedure per aspiration was calculated by dividing the total duration of the procedure by the number of aspirations. The ALDRETE score (global assessment of post-anesthetic condition) was used to assess patients' recovery after bronchoscopy.[15] The patients were evaluated at the end of the CP-EBUS for amnesia with a three-point Likert scale by the bronchoscopist. The Likert scale choices are as follows: I do not remember anything about the process; I remember something about the process, and I remember everything clearly about the process.[1] In addition, 30 minutes after the completion of CP-EBUS, the patients were asked to evaluate the cough, pain, dyspnea symptoms at the time of bronchoscopy with visual analog scale (VAS). The patients used a five-point Likert scale to rate their willingness to return for this procedure again in the future, if necessary. This scale was previously used to assess the tolerance of bronchoscopy.[1,14,16,17] The Likert scale choices are as follows: definitely not, probably not, unsure, probably would, and definitely would return.[1] The satisfaction of the patients and bronchoscopist about the procedure and sedation status were also questioned by a seven-item Likert type scale. Sedation or CP-EBUS-related complications, were also recorded and the procedure was completed.

Convex probe EBUS-guided transbronchial needle aspiration

The CP-EBUS-guided TBNA from hilar or mediastinal lymph nodes were performed after physical examination, chest X-ray, routine biochemical analysis, pulmonary function tests. Thoracic computed tomography or positron emission tomography-computed tomography were done as indicated. The EBUS-TBNA examination was performed in all patients at the Pulmonary Department as an outpatient procedure in a dedicated bronchoscopy suit with a 7.5 MHz, BF-UC160F (Olympus Optical CO. Tokyo, Japan) convex probe bronchoscope and EU C2000 processor (Olympus, Tokyo, Japan), by oral route and in supine position under local anesthesia with lidocaine and conscious sedation with intravenous (IV) midazolam (group M) or IV midazolam + fentanyl (group F). The EBUS-TBNA was performed to the mediastinal masses or lymph nodes for the diagnostic or staging purposes. A 22-gauge NA-201SX-4022-C needle (Olympus, Tokyo, Japan) was used for the procedure. During the process, the total number of aspirated lymph nodes and aspirations per patient, the total duration of the procedure were recorded, and the duration of procedure per aspirated lymph node and per aspiration for each patient were calculated and recorded.

Statistical analysis

Statistical analysis was performed using the PASW Statistics for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered statistically significant. The data were statistically compared using the Mann-Whitney U test.

RESULTS

There was no statistically significant difference in demographic characteristics between the two groups (Table 1). The CP-EBUS was performed for diagnostic, staging or both purposes at 16, six, and three patients in the group F and at 21, one, and three cases in the group M, respectively. The mean midazolam dose was 3.2±1.1 mg in the group M and 2 mg in the group F. The mean fentanyl dose was 60.2±21.3 μg in the group F. There was no statistically significant difference in the Ramsey sedation scale scores between the groups.

Cough symptom scores during the procedure evaluated by VAS were significantly less in the group F than the group M ($p<0.05$). The mean VAS score for cough symptom was 2.24±1.96 in the group M and 1.12±1.27 in the group F. There was no statistically significant difference in pain and dyspnea scores between the groups.

In the group F, 24 (96%) patients reported they would "definitely return" for EBUS-TBNA in the future, if required, and one (4%) patient reported he would "probably return" for such a procedure. On the other hand, in the group M, 23 (92%) patients reported they would "definitely return" for EBUS-TBNA in the future, if required, whereas two (8%) patients reported they would "definitely not return" for such a procedure.

The patient and bronchoscopist satisfaction levels were also found to be significantly higher in the group F ($p=0.007$, $p<0.0001$) (Figure 1). The mean scores for patient and bronchoscopist satisfaction were 6.40±0.87 in group M and 6.92±0.28 in group F and 5.44±1.83 in group M and 6.84±0.47 in group F, respectively.

Table 1. Demographic characteristics of patients in group M and group F

	Group M	Group F	
	Mean±SD	Mean±SD	*p*
Age (years)	47.2±16.1	55.2±12.2	0.20
Body weight (kg)	74.3±18.3	72.0±10.4	0.63
FVC (mL)	3444±90	3022±76	0.11
FVC (%)	93.7±14.6	84.0±15.5	
FEV_1 (mL)	2613±68	2261±62	0.07
FEV_1 (%)	85.9±12.8	76.3±13.4	
FEV_1/FVC	75.0±10.6	72.8±9.3	0.32
Midazolam dose (mg)	3.2±1.1	2	0.000*
Fentanyl dose (μg)	None	60.2±21.3	–
Ramsey	2.08±0.6	2.04±0.2	0.69
Amnesia	2.44±0.7	2.36±0.7	0.65

M: Midazolam; F: Fentanyl; SD: Standard deviation; FVC: Forced vital capacity; FEV_1: Forced expiratory volume in 1 second; * There was no statistically significant difference in the variables of two groups except the midazolam dose.

The most common aspirated lymph node stations were 7 (36), 4R (24), 11R (11), 4L (9) and 11L (9). Duration of procedure per aspirated lymph node was 9.65±3.14 minute in group M and 7.78±2.45 minute in group F. It was significantly lower in group F ($p<0.05$) and duration of procedure per aspiration was also shorter in the F group (4.99±2.01 vs 3.89±1.09) ($p=0.057$). There is no statistically significant difference in the total duration of process between the groups.

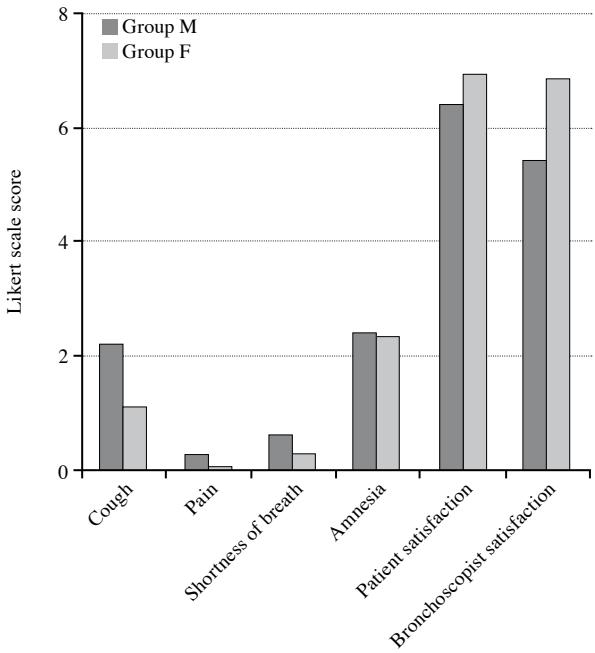

Figure 1. Distribution of symptoms during convex probe endobronchial ultrasound and satisfaction of patients and bronchoscopist in group M and group F. M: Midazolam; F: Fentanyl.

Minimum and maximum heart rate measured during the procedure and heart rate measured at the end of the procedure was significantly lower in group F than group M ($p=0.006$, $p=0.001$, $p=0.004$, respectively) (Table 2). However, no significant difference was found in minimum saturation measured during the procedure, systolic, and diastolic blood pressures before and after the procedure and the level of amnesia between the groups.

Bradycardia was detected in one patient at group M and hypotension was detected in one case at group F related to sedation and no intervention was required for these complications.

DISCUSSION

We compared the effects of midazolam and midazolam-fentanyl combination on CP-EBUS performed patients and bronchoscopist satisfaction, the patients willingness to return for this procedure again in the future, if necessary, the frequency of bronchoscopy-related symptoms, duration of the process, and level of amnesia. Our results indicate that combined use of midazolam-fentanyl is superior to midazolam for patient and bronchoscopist satisfaction. It also shortens the duration of the process per aspirated lymph node and decreases the degree of coughing during the process with no change in the level of amnesia.

Dreher et al.[18] reported that flexible bronchoscopy (FB) was better tolerated when the combination of midazolam and alfentanyl was used, compared to sedation with midazolam alone, although the total amount of midazolam administered was two-fold higher when midazolam alone was given. In our study, the patient and bronchoscopist satisfaction was also

Table 2. Comparison of midazolam and fentanyl groups

	Group M	Group F	
	Mean±SD	Mean±SD	*p*
Cough (score)	2.24±1.96	1.12±1.27	<0.05
Bronchoscopist satisfaction (score)	5.44±1.83	6.84±0.47	<0.001
Patient satisfaction (score)	6.4±0.87	6.92±0.28	0.007
Duration of procedure (min)	16.04±5.14	16.48±6.04	0.97
Duration of procedure per aspirated lymph node (min)	9.65±3.14	7.78±2.45	<0.05
Duration of procedure per aspiration (min)	4.99±2.01	3.89±1.09	0.057
Minimum pulse rate during procedure (pulse/min)	90.6±17.0	77.9±13.2	0.06
Maximum pulse rate during procedure (pulse/min)	123.5±17.3	104.6±16.3	0.04
Pulse rate at the end of the procedure (pulse/min)	101.8±19.0	87.1±12.8	0.01

M: Midazolam; F: Fentanyl; SD: Standard deviation.

found to be significantly higher in the group F. The mean midazolam dose in group M and group F was 3.2±1.1 mg (0-6), 2 mg, respectively in our study. Steinfort and Irving[1] evaluated the patient satisfaction during EBUS-TBNA under conscious sedation and they concluded that it might be associated with extremely high patient satisfaction. In the study of Yoon et al.,[19] it was demonstrated that the addition of alfentanil to propofol did not show any difference in patient or bronchoscopist satisfaction for sedation quality.

A total of 98% patients reported that they would repeat the process, if necessary, while 59% reported that they did not remember anything about the process in the study of Steinfort and Irving.[1] The authors revealed that the level of amnesia was significantly higher in the patients who received the combination of propofol than the combination of midazolam and fentanyl (p=0.001). In our study, 96% patients in the fentanyl plus midazolam group reported they would "definitely return" for the process, if required, whereas 4% patients reported that they would "probably return" for such a procedure. On the other hand, 92% patients in the group M reported that they would "definitely return" for process, if required, whereas 8% patients reported that they would "definitely not return" for such a procedure. Although amnesia levels of two groups were similar, these answers indicated that patients were able to remember more about the procedure in the midazolam group. In another study, Tekin et al.[20] compared the combined use of propofol and alfentanil with diazepam for sedation at FB process. All patients in the first group reported that they would prefer the same method, however, 80% of the second group reported that they would not prefer the same method.

In our study, although there were no statistically significant differences in pain and dyspnea scores between two groups, cough symptoms during the procedure were significantly lower in the group F. This finding can be explained by the anti-tussive effects of opioids.[19,21-24] In contrast, study of Yoon et al.[19] showed no difference in the degree of coughing between the propofol and propofol plus alfentanil groups. However, in their study, both groups showed much lower degree of coughing compared to the results from previous studies of sedation performed with midazolam or those of studies in which sedation was not administered.[19,25,26] The authors concluded that it might result from the anti-tussive effects of propofol itself.[19,26,27] In addition, Tekin et al.[20] demonstrated that cough symptoms were significantly lower in the propofol and fentanyl groups than the diazepam group.

Furthermore, duration of the procedure per aspirated lymph node was significantly lower in group F. Although duration of the procedure per aspiration was shorter in the F group as well, there was no statistically significant difference in the total duration of process and duration of procedure per aspiration in our study. In general, the EBUS-TBNA for mediastinal staging is a relatively longer procedure. More lymph node stations can be sampled by EBUS-TBNA in a shorter time period in well-sedated patients. Although the total number of the patients who underwent EBUS-TBNA for disease staging was higher in the group F than the group M (6 vs 1), the total duration of the process was similar in two groups.

In conclusion, the combination of fentanyl and midazolam shortens the duration of procedure and increases the patient and physician satisfaction compared to the use of midazolam alone without any significant difference in the rate of complications.

Declaration of conflicting interests

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