

# The role of using antitussive for premedication of bronchoscopy antitussive treatment in bronchoscopy: a randomized, double-blind, placebo-controlled trial

Nezihe Çiftaslan Gökşenoğlu<sup>1</sup>, Tülin Sevim<sup>2</sup>, Nilüfer Aykaç<sup>3</sup>, Emine Aksoy<sup>4</sup>

<sup>1</sup>Department of Intensive Care, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul, Türkiye

<sup>2</sup>Department of Chest Disease, Taksim Acıbadem University Hospital, İstanbul, Türkiye

<sup>3</sup>Department of Chest Disease, Altunizade Acıbadem University Hospital, İstanbul, Türkiye

<sup>4</sup>Department of Chest Disease, Süreyyapaşa Chest Diseases and Chest Surgery Training and Research Hospital, İstanbul, Türkiye

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## ABSTRACT

**Aims:** The cough affects adversely the comfort of patient and process during fiberoptic bronchoscopy. Various studies have been made to prevent cough during bronchoscopy. However, there is no any medication that usage of it becomes definite. The influence of usage codeine in bronchoscopy premedication in addition to the midazolam on the comfort of patient and physicians is examined .

**Methods:** 96 patients made bronchoscopy for various indications were included to the study. The study was carried out as a prospective, placebo-controlled and double-blind. The patients were divided into two groups. Group 1 (n=48) 20 mg fenocodeine tablets divided into 4 doses were administered one day before process. Group 2 (n=48) the placebo tablets divided four dose were administered one day before process. Both of two groups were administered midazolam before procedure. Topical anesthesia was administered as needed during the operation and its doses were recorded. Two questionnaire form that examined the level of comfort of patients and physicians, the amount of secretion and the severity of cough with a visual analogue scale (VAS) were prepared and they were immediately completed after procedure.

**Results:** In both groups, any complication wasn't occurred that require to terminate the process. In the scala evaluated by patients given fenocodein, the amount of cough was statistically significantly low (p=0.026). In the scale evaluated by doctors, the amount of secretion was lower (p=0.02). Comfort level of doctor was found significantly higher in Group 2 (p=0.02).

**Conclusion:** It was determined that the amount of secretion and cough had decreased and the level of comfort had increased when fenocodeine was given with midazolam prior to bronchoscopy

**Keywords:** Bronchoscopy, codeine, premedication

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## INTRODUCTION

Fiberoptic bronchoscopy (FOB) is an interventional process usually performed under topical anesthesia and appropriate sedation. It can be provided better toleration for patients with drugs administered before the process.<sup>1-5</sup>

During FOB cough adversely affects the comfort of patient and process. In studies to prevent cough that occurs during bronchoscopy, the effectiveness of various drugs were investigated. However, there is not any definitive medication have been resulted. Opioids; because of their analgesic, antitussive and anxiolytic effects are used as combination with other sedative agents in bronchoscopy.<sup>6</sup>

In this study, the group which was given codeine that has weak opioid property with midazolam was compared with the group

given midazolam alone. The effect of sedation on patients cough, secretion and level of comfort during the procedure was investigated.

## METHODS

Ninety-six patients performed bronchoscopy for various indications were included in the study. The study was performed as a prospective, placebo-controlled and double-blind. The study was carried out with the permission of İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital Scientific Researches Evaluation Ethics Committee (Date: 22.01.2013, Decision No: 1). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

**Corresponding Author:** Nezihe Çiftaslan Gökşenoğlu, neziheciftaslan@gmail.com

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### The Study Exclusion Criteria

Pregnant women, younger than 18 years old, patients who didn't give consent for bronchoscopy and /or patients with high risk or with contraindications for bronchoscopy, patients with contraindications for fenocodine and midazolam weren't included in our study.

The age, gender, smoking history, the comorbidities of patient, the indication for bronchoscopy, the arterial blood pressure values, the pulse measurement, the oxygen saturation in room air, the doses of topical anesthesia and midazolam were recorded.

Bronchoscopy was performed by 2 physicians. There were also 2 physicians during the procedures.

As a result the process and the amount of secretions evaluated the same bronoscopists.

10% lidocaine as a topical anesthesia was applied to the patient's nose and oropharynx by spraying. Lidocaine diluted with saline was applied to the trachea and bronchial system during the process. During bronchoscopy; blood pressure, pulse and oxygen saturation of the patients were monitored.

Midazolam was administered 1-2 mg as an initial dose considering age and weight of patients, at 5-10 minutes before procedure, it was administered as a 1 mg dose upon necessity.

Patients were randomized in two groups by bronchoscopy nurse. Doctor and patient were not aware of the patient's group.

Patients were divided into 2 groups.

Group 1: Group with midazolam and fenocodine tablets

Group 2: Group with midazolam and placebo

3 doses fenocodine each 20 mg tablet in 8 hours intervals were given to Group 1 patients one day before bronchoscopy and the fourth dose was given 2-3 hours before process. Three doses placebo were given to group 2 patients in 8 hours intervals one day before bronchoscopy and the fourth placebo tablet was given 2-3 hours before process.

Necessary diagnostic procedures were applied according to the lesions seen during bronchoscopy, all procedures performed and complications emerged during the process were recorded.

During the procedure, The Ramsey Sedation Scale was used to define the level of sedation of patient.

After the process was finished, the forms prepared for the patient and bronchoscopist were filled individually under the supervision of a bronchoscopy nurse.

It was charted from the patients and the doctors to mark the cough, secretion and degree of comfort on a visual analogue scale 100 mm in length. The highest values were located on the right side of the scale (100) and the lowest values were located on the left side.

### Statistical Analysis

Statistical Analysis: SPSS 16,0 software (Statistical Package for Social Sciences for Windows) was used for the statistical analysis of the data obtained from this study. Chi-square and Fisher's exact test were used for the comparison of qualitative data, student T-test was used for the comparison of quantitative data. Results were assessed at 95% confidence interval and significance was assessed as  $p < 0.05$

## RESULTS

Totally 96 patients were included to the study that 21 (21.9%) of them were female (21.9%), 75 (78.1%) of them were male. The mean age of the patients was  $56.9 \pm 1.4$  (range: 28-82 years).

The most common indication for bronchoscopy was lung cancer. The indications for bronchoscopy are shown in **Table 1**. The procedures performed during bronchoscopy are shown in **Table 2**.

**Table 1. The indications for bronchoscopy**

	Group 1 (Fenocodine n:48)	Group 2 (Placebo n:48)	Total (n=96)
Lung cancer	22	25	47
Tuberculosis	7	1	8
Interstitial lung disease	5	6	11
Hemoptysis	10	4	14
Solitary pulmonary nodule	1	2	3
Pneumonia	2	2	4
Tuberculosis+lung cancer	1	2	3
Pneumonia+lung cancer	0	2	2
Atelectasis	0	2	2
Pleural effusion	0	1	1
Cystic hydatid	0	1	1
Total	48	48	96

Patients were divided into 2 groups. In Group 1, there were 48 patients (50%), in Group 2 there were 48 (50%) patients. There was no significant difference in between two groups in terms of the distribution of age, gender and additional diseases (**Table 3**).

**Table 3. The distribution of age, gender, and the additional disease**

	Group 1 n (%)	Group 2 n (%)	P
Gender			0.8
Female	10 (20.8)	11 (22.9)	
Male	38 (79.2)	37 (77.1)	
Additional diseases	23 (51)	22 (49)	0,5
Age	$55.5 \pm 14.5$	$58.4 \pm 12.9$	0.3

**Table 2. Procedures in bronchoscopy**

	Group 1 (Fenocodine n:48)	Group 2 (Placebo n:48)	Total
Bronchial lavage	20 (41.7%)	10 (20.8%)	30 (31.2%)
Endobronchial biopsy+bronchial lavage	8 (16.7%)	15 (31.2%)	23 (24%)
Transbronchial biopsy	1 (2.1%)	0	1 (1%)
Transbronchial biopsy+bronchoalveolar lavage+bronchial lavage	2 (4.2%)	4 (8.3%)	6 (6.2%)
Endobronchial biopsy+transbronchial biopsy+bronchoalveolar lavage	1 (2.1%)	1 (2.1%)	2 (2.1%)
Endobronchial biopsy+bronchial lavage+brush	6 (12.5%)	2 (4.2%)	8 (8.3%)
Bronchoalveolar lavage+brush	8 (16.7%)	15 (31.2%)	23 (24%)
Endobronchial biopsy +transbronchial biopsy +bronchoalveolar lavage	1 (2.1%)	0	1 (1%)
Bronchial lavage+bronchoalveolar lavage	1 (2.1%)	1 (2.1%)	2 (2.1%)
Total	48	48	96

When two groups were compared in terms of bronchoscopy duration midazolam dose, local anesthetic dose and Ramsey Sedation Scale there was no significant difference between them (Table 4).

**Table 4. The comparison of the groups in terms of bronchoscopy time, midazolam dose, local anesthetic dose and the Ramsey Sedation Scale**

	All patients mean±SD	Group 1 mean±SD	Group 2 mean±SD	P
Bronchoscopy time (min)	11.2±4.6	11.4±5.2	11.06±4	0.709
Midazolam dose (mg)	2.12±0.5	2.1±0.5	2.2±0.5	0.225
Anesthetic dose (mg)	165±68.9	175±67.5	155±69.4	0.144
Ramsey Sedation scale	2.2±0.7	2.3±0.7	2.1±0.6	0.309

In the visual analogue scale that assessed by the patients, the amount of cough was 61.72±24.40 mm in Group 1, 50.39±24.56 mm in Group 2. The patients were given fenocodein showed the amount of cough much less than the group were given with placebo. The difference between two groups was statistically significant ( $p<0.02$ ) (Table 5).

**Table 5. The comparison of the visual analog scale scores of the groups**

Patient	Fenocodein (Grup1) mean±SD	Placebo (Grup 2) mean±SD	P
Secretion (mm)	62.72±24.88	53.66±22.68	0.065
Cough (mm)	61.72±24.40	50.39±24.56	0.026
Comfort (mm)	61.60±23.12	55.25±20.94	0.16

In the visual analog scale assessed by the doctors, the amount of secretion in Group 1 patients given fenocodein was 65±15.27 mm and in Group 2 received placebo was 57.04±18.60 mm. Accordingly in the group given fenocodein the amount of secretion was much less, but the difference between the two groups was not statistically significant ( $p=0.02$ ).

The comfort of the doctors was 61.93±22.20 mm in Group 1 and 51.52±22.98 mm in Group 2 respectively. Accordingly, in Group 1 the comfort level of the doctor was evaluated more higher, the difference between the two groups was statistically significant ( $p=0.02$ ).

In both groups, a complication hasn't developed to require the termination of the process.

## DISCUSSION

It is aimed that to increase the comfort of the patient and physician (cough, secretion, dyspnea sensation, patient compliance, process duration, etc.) and to reduce drug use for sedation and to take the best results for the process by using the premedication before bronchoscopy.

Several opioid antitussive drugs were investigated as well as to suppress the cough, but failed to reach a definitive conclusion for the routine use of these drugs.<sup>7-11</sup>

The most common drugs used for sedation are benzodiazepines, propofol, and opioids.<sup>6</sup>

Midazolam is preferred by doctors because of the rapid half-life time and affecting short duration.<sup>12</sup> Although this drug makes the process easier in many ways, it has no effect on cough and secretion.

Opioids are used in pain management for many years; analgesic, antitussive and anxiolytic effects. This group of drugs preferred to use alone due to the short half-life and rapid start-up period,

is limited during bronchoscopy, they are used in combination with other analgesic agents.<sup>13-15</sup>

Haga T et al.<sup>16</sup> have performed bronchoscopy by applying deep sedation. In this study, patient satisfaction was evaluated. No significant difference was found between the two groups with and without deep sedation applied with midazolam.

There are several studies, that is about addition to midazolam, other sedative drugs.

Some studies show that the more effective the co-administration of the agent than the administered alone.<sup>17,18</sup>

The apply of midazolam and opioid or propofol reduce the amount of cough and reduce the dose of topical anesthetic. Thus they increase the patient tolerance.<sup>19,20</sup>

In the study by Crawford et al.<sup>21</sup> were compared with a group given propofol and midazolam to a group given fentanyl. In this study, the advantages of rapid onset and short duration of propofol have been reported. However it is recommended that propofol should be used for patients requiring deep sedation and it should be used under the responsibility of the anesthesiologist.<sup>6</sup> But opioids can be used safely by the bronchoscopist.

In a study of Tsunozuka et al.<sup>22</sup> in 1999; patients received midazolam were divided into 2 groups; as a group given a placebo and the other group given codeine phosphate. Finally it was determined that the necessity of local anesthesia was less in the group given codein. This finding was interpreted because of developing cough less in the group given codein.

Tsunozuka et al. claimed that the administration of opioid with midazolam is beneficial for both the patient and the doctor.

As there was no significant reduction in the need of local anesthesia in our study, the results of this study supports that cough is less in the group given codein when it is assessed by visual analog scale.

In the Tsunozuka and his colleagues study codein was given 60 minutes before process. The half-life of Codeine phosphate is 2-3 hours. Also to reach maximum concentration in plasma a drug must be given until 4-5 half-life time. Therefore in our study fenocodein tablets given were initiated the day before process, 20 mg fenocodein tablets were given at 8 hours intervals three times and the final dose was given 2 hours before process. Thus, it was intended to reach the highest concentration in plasma.

In another study done by Stolz et al.<sup>23</sup> in 2004, midazolam and hydrocodone 5 mg IV had been administered to one group patients, midazolam and placebo had been administered to another group patients. As a result of the study; it was reported that in the group given midazolam and hydrocodone the less cough and the better patients tolerance.

Although the antitussive effect of codeine is less than hydrocodone, it is very important that our study determines that in the group given codein cough is less.<sup>24</sup>

The oral use, the any side effects no seen, the easy achievability of codeine in our country, show that it can take place as a cough-reducing drug in our bronchoscopy practice.

In the study of Stolz et al.<sup>19</sup> with Tsunozuka et al.<sup>22</sup> it wasn't specified that there was no significant decrease in the oxygen saturation levels in the group given opioid. In our study, no significant difference was developed in oxygen saturation level during process for both groups too.

## CONCLUSION

As a result of our study, it has been indicated that the addition of oral fenocodein to the midazolam sedation reduced cough and increased the comfort of the patient and the physician and not caused any side effects extension. Therefore it was concluded that fenocodein is an effective and reliable drug that can be used to decrease the cough during the bronchoscopy process. It is convinced that fenocodein can be used routinely before bronchoscopy process after the results of other major studies that will be made in the future.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital Scientific Researches Evaluation Ethics Committee (Date: 22.01.2013, Decision No: 1).

### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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### Author Contributions

All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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