The Effect of Dextromethorphan Premedication on Cough and Patient Tolerance During Flexible Bronchoscopy

A Randomized, Double-blind, Placebo-controlled Trial

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Background: **Patients undergoing bronchoscopy can experience problems such as anxiety and cough, requiring various doses of sedatives and analgesics. The purposes of this study were to investigate the effect of premedication with dextromethorphan on patients' cough and anxiety, and the use of analgesics/sedatives during flexible bronchoscopy (FB).**

Methods: **A randomized, double-blind, placebo-controlled, prospective study was performed to assess the effect of dextromethorphan premedication on patients who underwent diagnostic bronchoscopy. Seventy patients included in this study were randomly allocated into 2 groups: group A consisted of 35 patients who received dextromethorphan before FB; and group B consisted of 35 patients who received a placebo. A questionnaire was given to the patients and bronchoscopist about perception of cough, anxiety, and discomfort. The amount of sedative medication and lidocaine use during the procedure and the procedure time were recorded.**

Results: **The group that was premedicated with dextromethorphan had lower complaint scores, significantly less coughing, significantly less stress assessed by the patient and the physician evaluation, shorter total procedure time, and fewer midazolam requirements during FB (P-value < 0.05).**

Conclusion: **Considering its safety profile, dextromethorphan premedication is an effective approach to facilitate the performance of FB for the physician, and could improve patient comfort.**

Key Words: dextromethorphan, premedication, bronchoscopy, cough, patient tolerance

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Bronchoscopy is one of the most common procedures used in pulmonary medicine, and allows evaluation of the respiratory tract with minimal invasiveness. Nevertheless, most patients undergoing bronchoscopy experience some complications, such as fear of pain, difficulty breathing, nasopharyngeal irritation, and cough.[1,2] Although moderate sedation is generally used during bronchoscopy to facilitate its performance for the bronchoscopist, these regimens have variable impact on patient comfort, procedure tolerance, and cough suppression.[3,4] Despite the use of sedative and analgesic medication during the procedure, some patients express discomfort, and have severe cough and body movements. Thus, using premedication may have favorable effects, including sedation, reduction of patient discomfort, and improved procedure tolerance.[5,6]

Dextromethorphan is frequently used as an antitussive medication, and we examined whether the use of premedication with dextromethorphan allows more convenient performance of flexible bronchoscopy (FB). The primary objectives of this trial were to investigate the effects of dextromethorphan premedication on patients' cough and anxiety and to explore analgesic/sedative use during FB.

PATIENTS AND METHODS

A prospective, randomized, placebo-controlled clinical trial was conducted at Vali-Asr Hospital, a tertiary university hospital of Tehran University of Medical Sciences. The study protocol was approved by the Ethics Committee of Tehran University of Medical Science, and informed written consent was obtained from all the participants after registration in the study (IRCT ID: IRCT2015060520024N2).

Patients who were undergoing FB due to productive cough, hemoptysis, bronchogenic neoplasm, or lung infection were included in this

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study. Those scheduled for FB in this study were randomly assigned to group A (dextromethorphan) or group B (placebo) according to the 4 blocks (AABB) randomization system. An independent nurse prepared vials containing dextromethorphan or a placebo. These vials could not be distinguished because they were the same size and shape and held the same volume of liquid. Only the main supervisor of the study was aware of the exact drug/placebo groups. The patient, main physician, bronchoscopy staff (including the bronchoscopist and anesthetist), and researcher were blind to the drug/placebo groups. Patients with a history of hypersensitivity to dextromethorphan, those unwilling to participate, patients with a history of sedative medication use (including opioids, benzodiazepines, and psychotropic medications) within 12 hours before the procedure, and pregnant and breastfeeding women were excluded from the study (Fig. 1).

A flexible flexible bronchoscope (Olympus BF-1T30, 1T200; OD, 6 mm) was used to perform the bronchoscopies. The patients in the dextromethorphan group received dextromethorphan syrup 90 mg, 60 minutes before bronchoscopy, whereas the patients in the placebo group received a placebo. All patients received 4 mL of nebulized 2% xylocaine just before bronchoscopy. Moderate sedation was achieved with a combination of midazolam and fentanyl under the supervision of a pulmonologist. If the patients exhibited severe cough during FB, intrabronchial supplemental local anesthesia (1% lidocaine solution) was instilled by the bronchoscope to the trachea and segmental bronchi to suppress the cough. The dose of supplemental local anesthesia required was noted for each patient. Electrocardiogram, pulse oximetry, and vital signs were monitored during bronchoscopy.

A visual analog score for cough, feeling of unpleasantness, and stress level assessed before and after the examination by the patient and the physician was used. The cough score rated cough severity by numbers 1 and 2 as a slight cough,

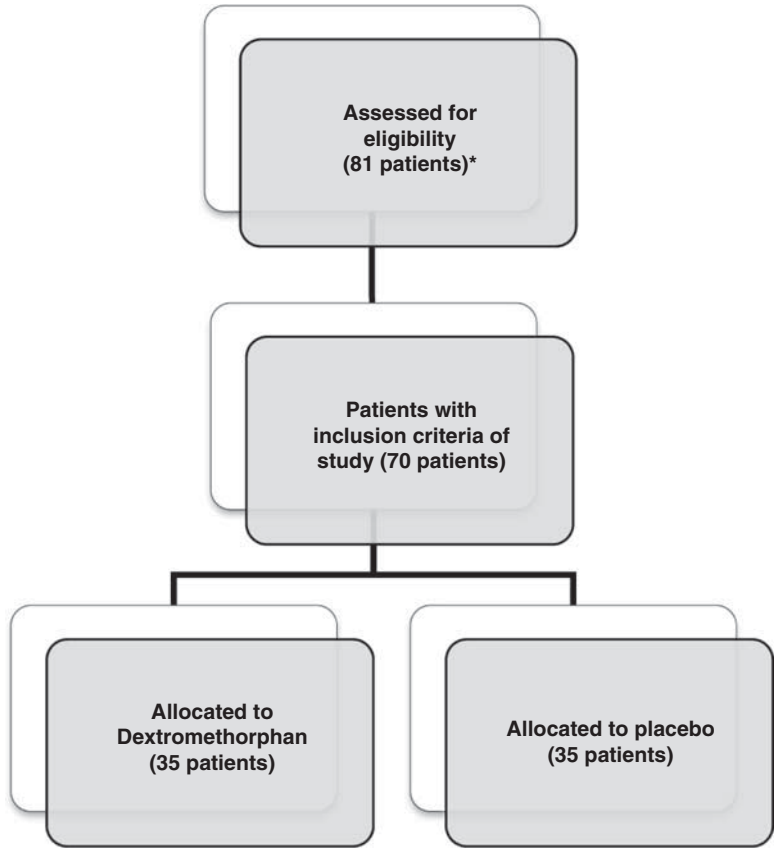

FIGURE 1. Consort flowchart of the study. *Seven patients with history of sedative medication use and 4 patients unwilling to participate in the study were excluded

TABLE 1. Comparison of Baseline Demographics Features in Dextromethorphan and Placebo Group

	Dextrometorphan	Placebo	*P*
Sex [n (%)]			0.45
Male	21 (60%)	24 (69%)	
Female	14 (40%)	11 (31%)	
Age (mean ± SD)	52 ± 2.1	51 ± 2.3	0.42
Past medical history [n (%)]			
Nothing	16 (45.7)	20 (57)	0.35
Malignancy	3 (8.6)	5 (14.3)	0.58
Hypertension	2 (5.7)	5 (14.3)	0.23
CHF	5 (14.3)	5 (14.3)	1.00
IHD	3 (8.6)	1 (2.9)	0.30
Diabetes mellitus	1 (2.9)	3 (8.6)	0.30
Obstructive pulmonary disease	5 (14.3)	3 (8.6)	0.45
TB	1 (2.9)	1 (2.9)	1.00
Indications for the bronchoscopy [n (%)]			
Suspected infection	22 (62.8)	21 (60)	0.81
Suspected malignancy	7 (20)	6 (17.1)	0.76
Miscellaneous causes	6 (17.1)	8 (22.8)	0.55

CHF indicates congestive heart failure; IHD, ischemic heart disease; TB, tuberculosis.

number 3 as a moderate cough, number 4 as a severe cough, and number 5 as a very severe cough.

The data were analyzed using SPSS version 18.0 software. Student *T* test and analysis of variance tests were used to compare the patient tolerance, cough numbers, and other continuous variables between the 2 groups. For comparing categorical variables, χ^2 testing was used. For all statistics, a *P*-value of <0.05 was considered statistically significant.

RESULTS

A total of 70 patients were included in the study, 35 of whom received dextromethorphan, and 35 of whom received a placebo. There were no significant differences between the dextromethorphan group and the placebo group in terms of age, sex, medical history, and bronchoscopy indication (Table 1). Table 2 shows evaluation of cough scores and stress levels. The mean dose of intravenous midazolam given during FB was significantly lower in the dextromethorphan group compared with the placebo group (5.0 ± 0.1 vs. 9.5 ± 2.8 mg midazolam, respectively). However, the mean doses of lidocaine and fentanyl given during FB were not significantly different (Table 2). The total procedure time was also significantly lower in the dextromethorphan group compared with the placebo group (10.8 ± 3.3 vs. 14.7 ± 3.7 min, respectively; $P < 0.05$).

TABLE 2. Cough Score Evaluation by Physician/Patient and Patient's Anxiety Assessed by Physician, During and After Flexible Bronchoscopy and Sedative/Analgesic Drug Use in Dextromethorphan and Placebo Group

	Dextromethorphan Group	Placebo Group	*P*
Cough evaluation by physician during FB	2.23 ± 0.88	4.33 ± 0.83	< 0.05
Cough evaluation by patient during FB	1.95 ± 0.75	4.13 ± 0.93	< 0.05
Cough evaluation by physician after FB	2.50 ± 0.93	4.50 ± 0.76	< 0.05
Cough evaluation by patient after FB	2.04 ± 0.70	4.03 ± 0.83	< 0.05
Stress evaluation by physician during FB	2.04 ± 0.71	3.94 ± 081	< 0.05
Stress evaluation by physician after FB	2.03 ± 0.70	3.94 ± 1.07	< 0.05
Fentanyl use during FB (μg)	114.6 ± 26.1	117.1 ± 34.2	0.68
Midazolam use during FB (mg)	5.0 ± 0.1	9.5 ± 2.8	< 0.05
Lidocaine use during FB (mg)	250.1 ± 100.1	277.8 ± 44.1	0.48

Values are presented as means ± SD.

Subjective scoring was obtained by using visual analogue score rating from 1 = mildest to 5 = most severe.

FB indicates flexible bronchoscopy.

DISCUSSION

In this randomized clinical trial, we evaluated the impact of dextromethorphan premedication on ease of performing FB, patient anxiety, and cough score during the procedure. According to bronchoscopy guidelines, premedication for bronchoscopy is not routinely indicated, and intravenous sedation should be administrated to patients undergoing bronchoscopy, except in cases of contraindication.[7,8] Studies have shown that sedation can influence comfort, tolerance, and bronchoscopic ease.[9–11] On the basis of a survey in the United Kingdom, a midazolam and fentanyl combination was the most frequently used combination sedation used by bronchoscopists.[9] The use of an opioid in addition to Midazolam improves cough, and reduces lidocaine use.[12,13] However, the risk of complications, such as oversedation, may

be increased, especially in older patients and patients with concomitant disease.

Schwarz et al[6] conducted a randomized control trial comparing dextromethorphan premedication with placebo. They found that dextromethorphan is an effective bronchoscopic premedication that improves the overall well-being of the patients. In their study, they used midazolam alone as sedative drug during the procedure. However, based on the most recent British Thoracic Society guidelines (2013) regarding diagnostic flexible bronchoscopy in adults, a combination of opioid (such as fentanyl) and midazolam is recommended to improve bronchoscopic tolerance.[7] The use of benzodiazepines combined with opioids is suggested because of the synergistic effects on patient tolerance during the procedure and the added antitussive properties of the opioids. To the best of our knowledge, there was no randomized control trial before this study to compare the effect of dextromethorphan premedication with placebo in FB by using more intense sedation (combination of benzodiazepines and opioids). The current study investigated whether dextromethorphan premedication is still effective in the setting of using a benzodiazepine and opioid combination during FB. With the increasing use of opiates, which have central cough suppressant effects, and their potential serious clinical toxicity, there is a need for evidence regarding the efficacy of dextromethorphan premedication (as a safe and cost-effective medication). Similar to the previous study,[6] we found no difference in lidocaine mean dose between the 2 groups. In contrast to a previous study that did not use an opioid during FB, we also used fentanyl. However, the dose of fentanyl used in the dextromethorphan premedication group was not significantly lower compared with the dose used in the placebo group. This could possibly be due to a difference in preferred analgesic/sedation level by our bronchoscopist, or the low number of patients in this study, preventing these differences from reaching statistically significant values. Meanwhile, dextromethorphan is not a sedative medication per se, which could also explain why the standard dose of opioid/analgesic was still required during the procedure.

An important issue in this study is the high dose of benzodiazepine that was used in the placebo group for suppression of symptoms during FB. The usual dose of midazolam during FB is 0.06 to 0.7 mg/kg,[14–16] and according to some studies, higher doses did not show a significant advantage.[17]

Midazolam is the sedative drug of choice during FB because of its benefits, including antegrade amnesia, patient comfort/tolerance, and bronchoscopist performance.[8] Although opioids (including fentanyl) do not have these advantages, the combination of midazolam and fentanyl is now a preferred sedation choice for FB. By post hoc analysis of our investigation, it is evident that the fentanyl was underused compared with the more liberal use of midazolam. It could be due to inappropriate systematized monitoring of patients' level of sedation during the procedure and the bronchoscopist's preference of midazolam over fentanyl due to its better and more rapid effect on patients' calmness and tolerability of procedure. However, it must be kept in mind that underusing fentanyl as an opioid with antitussive effects could have a positive effect on patients' cough,[18] possibly affecting our study outcomes. Another limitation of our study was that assessment and quantification of sedation depth by standard tools was not performed. Furthermore, patient desire to undergo a repeat procedure was not evaluated.

CONCLUSIONS AND RECOMMENDATIONS

Despite the fact that this study was not a multicenter study and had a low number of patients, we found that cough, patient anxiety, and midazolam use during FB were significantly less marked with dextromethorphan premedication. Procedure time was also significantly lower in this group compared with the placebo group. Considering that dextromethorphan was well tolerated and had the proper effect on symptoms as reported by patients and physicians, as well as reducing midazolam use and procedure duration, we recommend premedication with dextromethorphan in FB, especially in those patients for whom procedure duration and/or amount of benzodiazepine dose are important.

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