Effectiveness of combined use of formoterol fumarate tablets and interventional bronchoscopy in the treatment of central airway tumor

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Abstract

Purpose: To study the effectiveness of formoterol fumarate tablets when used in combination with interventional bronchoscopy for central airway tumor.

Methods: A total of 154 central airway tumor patients on admission in Second Affiliated Hospital of Zunyi Medical University, Zunyi, China (August 2020 - December 2022) were assigned to benign group (BG, n = 70) and malignant group (MG, n = 84), based on the nature of tumor lesion. The patients were administered formoterol fumarate tablets as well as interventional bronchoscopy. Clinical efficacy, lung function indices such as forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC ratio, blood gas indices (pH, partial pressure of oxygen (PaO2) and partial pressure of carbon dioxide (PaCO2)), scores on shortness of breath, and survival rate, were determined and compared between the two groups.

Results: The overall effectiveness in BG (97.14 %) was significantly higher than that in MG (84.52 %). There were higher post-treatment values of FEV1, FVC and FEV1/FVC; higher values of pH and PaO2, lower PaCO2, and lower scores on shortness of breath in BG and MG, relative to pre-treatment levels (p < 0.05). Follow-up showed no recurrence in patients with benign tumor, and clinical efficacy was satisfactory. The 2-year survival rate of patients with malignant tumor was 51.19 %.

Conclusion: The combination of formoterol fumarate tablets and interventional bronchoscopy produces significant curative effect on benign and malignant tumor in central airway. It improves lung function, blood gas indices and survival rate, and mitigates shortness of breath. Therefore, this treatment strategy has a high potential for use in clinical practice.

Keywords: Formoterol fumarate tablets, Interventional bronchoscopy, Central airway tumor, Clinical efficacy

INTRODUCTION

A statistical survey has revealed that the incidence of central airway tumor, a lesion in trachea, principal bronchus, or bronchus of right middle section, is increasing year by year [1]. The disease is classified as malignant or benign, but the symptoms are severe. Most patients have...
vessel obstruction due to increased tumor volume, resulting in multiple pathophysiologic changes such as atelectasis, obstructive pneumonia and dyspnea, which constitute severe threats to the survival of subjects [2,3]. Thoracotomy was mainly used in the past, but it is difficult to treat central airway tumor. With the rapid advancements in medical techniques and respiratory technology, interventional bronchoscopy has become an effective strategy for treatment of airway tumor [4,5]. Interventional bronchoscopy, a popular and recognized treatment method, is a minimally invasive procedure that quickly relieves airway obstruction and mitigates clinical symptoms (e.g. dyspnea), with fewer complications and good tolerance, resulting in good quality of life for patients after surgery [6,7]. Formoterol fumarate tablets are used mainly for the treatment of bronchial diseases. The drug enhances bronchial dilation and relieves the symptoms of airflow limitation in respiratory tract by directly exciting bronchial β2-receptors and producing a strong and lasting anti-asthmatic effect. Formoterol produces a significant effect in the treatment of dyspnea caused by airway obstructive diseases [8]. A study has shown that formoterol fumarate tablets improved lung function and reduced inflammatory response in elderly patients with chronic wheezing bronchitis [9]. However, from the current literature on clinical studies, there are limited studies on the effectiveness of use of formoterol fumarate tablets in combination with interventional bronchoscopy in patients with central airway tumor. Therefore, this study was done to investigate the clinical efficacy of formoterol fumarate tablets used in combination with interventional bronchoscopy for central airway tumor, in order to provide reference data for clinical practice.

METHODS

General information on patients

In this retrospective investigation, one hundred and fifty-four patients with central airway tumor on admission in Second Affiliated Hospital of Zunyi Medical University, Zunyi, China from August 2020 to December 2022 were assigned to benign group (BG, n = 70) and malignant group (MG, n = 84), based on the nature of tumor lesion. The BG had 41 men and 29 women in the age range of 34 - 68 years (mean age = 51.86 ± 9.87 years), while the MG had 52 men and 32 women in the age range of 33 - 67 years (mean age = 50.52 ± 9.39 years). In terms of tumor classification, in BG, there were 22 cases of villous tumor, 13 cases of polyp, 6 cases of hemangioma, 7 cases of neurofibroma, 10 cases of leiomyoma, and 12 cases of hamartoma. MG had 23 cases of tracheal invasion of esophageal cancer, 18 cases of bronchial lung cancer, 12 cases of adenoid cystic carcinoma, 14 cases of tracheal invasion of thyroid cancer, 13 cases of squamous cell carcinoma, and 4 cases of typical carcinoid.

Inclusion and exclusion criteria

Patients who were diagnosed using bronchoscope, CT and histopathological examination; those who presented clinical manifestations such as cough, expectoration, asthma, dyspnea and hemoptysis; those with complete clinical data, and those with good cognitive function and high compliance, were included. Patients in the following categories were excluded: those who had dysfunctions in heart, liver and kidney; those with malignant tumor and other airway diseases, patients who had mental disorders and inability to communicate with others, those with congenital anomalies in bronchus and lungs, subjects with coagulation disorders, those with other organic diseases, and patients who were pregnant or lactating.

Ethical approval

This research was approved by Guizhou Provincial Health Commission, China (approval no. bgzwhk2021-087). Signed informed consent was obtained from patients and their family members who were fully aware of the purpose of this study which was executed in line with the principles of Helsinki [10].

Treatments and procedures

All patients received combination of formoterol fumarate tablets and interventional bronchoscopy. In addition, BG was treated with high-frequency coil and carbon dioxide cryotherapy. Formoterol fumarate (Astellas Pharma Inc; NMPA approval no: H20010434; strength: 40 µg/tablet given at a dose of 2 tablets, twice a day.

Treatment using a high-frequency coil

The instrument used was high-frequency electric knife (type: VIO200S) in ERBE. Fiberoptic bronchoscopy was inserted from the nasal cavity, and a high-frequency electric knife was connected to an electric snare, with patients in the supine position. At the front end of benign tumor with pedicel in the airway, the tumor base was ligated with the help of electric snare, with electric coagulation and electric power at 40 W.
Thereafter, the tumor tissue was removed through switching on of the electric switch and tightening of the electric snare. If the base of tumor was wide and thick, the resection was done with a high-frequency electric knife. For carbon dioxide cryotherapy, bronchoscopy was placed approximately 0.5 cm from the upper end of patients’ tumor. A soft cryoprobe was inserted into the lesion through the hole of bronchoscopic biopsy, and the metal end of the cryoprobe was placed at the edge of the tumor, thereby forming an ice ball at the top of the probe, so as to freeze the tumor for about 5 min prior to removing the tumor directly. MG was treated with argon plasma coagulation (APC) and stent embedding. If patients’ malignant airway tumor showed invasive growth at the base, APC was used to burn the tumor tissue. The argon jet nozzle was inserted into the bronchoscopic treatment hole, approximately 1 cm near the lesion, and then the pedal switch was repeatedly turned on along the tissue surface of tumor, with burning depth of 2 - 3 mm. In the implementation of treatment, special attention was paid to the reduction of oxygen concentration in the airway to prevent airway combustion and provide protection for the patient. For stent embedding, when the patient was in supine position, the fiberoptic bronchoscopy was inserted into the airway so that the guide wire was placed along the biopsy hole, and then the plunger was slowly inserted into patients’ airway. The plunger was placed along the guide wire to allow for better adjustment of the stent position and to ensure the accuracy of stent placement.

Evaluation of parameters/indices

The clinical efficacy (TE) was analyzed using the following evaluation criteria: if the resection of tumor tissue was more than 65 %, the treatment was markedly effective (ME). If the resection of tumor tissue was 35 - 65 %, the treatment was effective (E). If the resection of tumor tissue was less than 35 %, the treatment was ineffective. Treatment efficacy (TE) was calculated as shown in Eq 1.

\[ \text{TE} \text{%} = \left( \frac{\text{ME}+\text{E}}{T} \right) \times 100 \]

where \( T \) = total population of patients

Lung function indices

Indices such as FEV1, FVC and FEV1/FVC, were evaluated. The Scoring Criteria for Shortness of Breath formulated by the American Thoracic Society [11] was used to access shortness of breath, and the specific evaluation criteria were as follows: grade 1 was for patients who had shortness of breath when walking fast; grade 2 patients experienced breathlessness when they walked at normal rate; grade 3 comprised patients who had to stop walking at normal speed due to shortness of breath, while grade 4 consisted of patients who had shortness of breath during mild activities. The higher the score, the more severe the shortness of breath. Blood gas analysis was performed. Peripheral arterial blood (3 mL) was collected before and after treatment, and a special gas sensing electrode (Shanghai Lingfa Mechanical and Electrical Equipment Co. Ltd.; model: carbon dioxide AS35CG201) was used to measure pH, PaO2 and PaCO2.

Follow-up visits

The patients were followed up for 2 years to monitor the prognosis and determine survival rate by telephone and outpatient visit in door-to-door manner.

Statistical analysis

The data obtained in this study was processed with SPSS 26.0 software package, while GraphPad Prism 7 and SPSS were applied for plotting graphs. Data from enumeration and measurements are presented as n (%) and mean ± standard deviation (SD), and statistical analyses were done using \( \chi^2 \) test and \( t \)-test, respectively. Statistical significance was assumed at \( p < 0.05 \).

RESULTS

Treatment efficacy

Table 1 shows that overall treatment effectiveness was significantly higher in BG (97.14 %) than in MG (84.52 %).

Lung function indices

In BG and MG, there were significantly increased post-treatment levels of FEV1, FVC and FEV1/FVC (\( p < 0.001 \)), as shown in Table 2.

Shortness of breath

Before and after treatment, the scores on shortness of breath in BG were 3.04 ± 0.73 and 1.84 ± 0.69 points, respectively, while the corresponding scores in MG were 3.08 ± 0.68 and 1.96 ± 0.68 points, respectively (Figure 1). The scores on shortness of breath were lower after treatment than before treatment.
Table 1: Clinical treatment effectiveness in patients with benign and malignant tumors [n (%)]

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Markedly effective</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Overall effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG</td>
<td>70</td>
<td>58 (82.86)</td>
<td>10 (14.29)</td>
<td>2 (2.86)</td>
<td>68 (97.14)</td>
</tr>
<tr>
<td>MG</td>
<td>84</td>
<td>49 (58.33)</td>
<td>22 (26.19)</td>
<td>13 (15.48)</td>
<td>71 (84.52)</td>
</tr>
</tbody>
</table>

χ² = 6.916
P-value = 0.009

BG, benign group; MG, malignant group

Table 2: Pre- and post-treatment levels of lung function indices in patients with tumors (mean ± SD)

<table>
<thead>
<tr>
<th>Period</th>
<th>FEV1 (L)</th>
<th>FVC (L)</th>
<th>FEV1/FVC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign tumor group (n = 70)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>1.35±0.15</td>
<td>2.02±0.22</td>
<td>65.41±3.03</td>
</tr>
<tr>
<td>After treatment</td>
<td>2.30±0.41</td>
<td>2.80±0.35</td>
<td>77.30±2.83</td>
</tr>
<tr>
<td>t</td>
<td>18.402</td>
<td>15.823</td>
<td>23.989</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Malignant tumors group (n=84)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-treatment</td>
<td>1.39±0.14</td>
<td>2.04±0.28</td>
<td>64.86±2.79</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>2.08±0.40</td>
<td>2.62±0.27</td>
<td>75.38±2.40</td>
</tr>
<tr>
<td>t</td>
<td>14.841</td>
<td>13.617</td>
<td>26.209</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3: Blood gas data of patients with tumors before and after treatment (mean ± SD)

<table>
<thead>
<tr>
<th>Period</th>
<th>pH</th>
<th>PaO2 (kpa)</th>
<th>PaCO2 (kpa)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign tumor group (n=70)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>7.32±0.05</td>
<td>7.98±1.09</td>
<td>6.64±0.80</td>
</tr>
<tr>
<td>After treatment</td>
<td>7.40±0.03</td>
<td>12.30±0.70</td>
<td>5.37±0.39</td>
</tr>
<tr>
<td>t</td>
<td>11.279</td>
<td>28.020</td>
<td>11.876</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Malignant tumors group (n=84)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before treatment</td>
<td>7.30±0.04</td>
<td>7.84±1.05</td>
<td>6.68±0.83</td>
</tr>
<tr>
<td>After treatment</td>
<td>7.41±0.03</td>
<td>11.64±0.80</td>
<td>5.60±0.50</td>
</tr>
<tr>
<td>t</td>
<td>17.162</td>
<td>8.820</td>
<td>4.405</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Blood gas data

After treatment, there were significantly higher levels of pH and PaO2, and lower PaCO2 levels in BG and MG (p < 0.05). These results are presented in Table 3.

Survival status of patients with benign and malignant tumor

Seventy patients with benign tumor had no recurrence. In-patient observation and re-treatment were implemented for 2 patients whose treatments were ineffective, and satisfactory efficacy was observed after a 2-year follow-up. The same procedures were implemented among the 84 malignant tumor patients, for subjects whose treatments were ineffective. There were 43 survivors, and the 2-year survival rate of patients was 51.19%. These data are shown in Figure 2.
DISCUSSION

In recent years, with increasing incidence of lung tumor, the incidence of malignant tumor in central airway has gradually increased [12,13]. Central airway tumor presents different clinical symptoms at various stages.

In the early stage, irritable cough and low level of phlegm are usually seen. With disease progression, narrowing of airway diameter and decreased patency of airway occur. These lesions are characterized by chest distress and shortness of breath, dyspnea, stridor, and other symptoms. The airway-related symptoms become more obvious when the disease develops to the late stage, with some symptoms such as hoarseness, dysphagia, and tracheoesophageal fistula. Finally, following the development of malignant tumor, tumor metastasis occurs, a situation which threatens the survival of the affected patients [14-16].

In the past, treatment of airway tumor usually involved the use of conventional surgical methods such as tracheal segment resection and tracheal reconstruction. However, these procedures have some shortcomings such as large surgical trauma, multiple complications and poor prognosis, all of which affect the clinical efficacy, although the treatment effect is good [17]. The rapid advancements in bronchoscopy and endovascular interventional techniques have led to development of interventional bronchoscopy which is composed of high-frequency electrosurgical snare, stent implantation, argon plasma coagulotomy and carbon dioxide cryotherapy. Interventional bronchoscopy has been widely used in airway tumor. It is a common method used for patients with airway tumor due to its advantages of reduced trauma, lower treatment risk, fewer complications, relatively simpler operation, and lower cost, when compared to traditional surgery [18,19]. A study has shown that interventional cryotherapy using bronchoscopy effectively reduced the recurrence rate of patients with airway tumor, and enhanced the sensitivity of bronchial central malignant tumor to radiotherapy and chemotherapy [20]. Formoterol fumarate tablets and β2 receptor agonists are widely used in the treatment of dyspnea caused by airway obstructive diseases such as bronchial asthma, chronic bronchitis, asthmatic bronchitis and emphysema. The drug relaxes bronchial smooth muscle, and relieves bronchial smooth muscle spasm and anti-allergic reaction by directly exciting the bronchial β2 receptor and producing a strong and lasting anti-asthmatic effect. Therefore, in this study, the clinical efficacy of combined use of formoterol fumarate tablets and bronchoscopy intervention was investigated.

The data obtained in the present research revealed significantly higher total treatment effectiveness in BG than in MG. Therefore, the combination of formoterol fumarate tablets and interventional bronchoscopy played a significant role in the treatment of central airway tumor by producing a better treatment effect on benign tumor than on malignant tumor. This study has shown that interventional bronchoscopy significantly alleviated clinical symptoms of airway tumor through mitigation of chest discomfort, poor breathing and shortness of breath [21]. Central airway stenosis caused by the growth, infiltration and compression of central airway lesions in airway is usually manifested as changes in lung function indices, i.e. FEV1, FVC, and FEV1/FVC ratio. The post-treatment values of FEV1, FVC and FEV1/FVC ratio were elevated in BG and MG, relative to the pre-treatment values, and the scores on shortness of breath decreased after treatment. These results suggest that the combination of formoterol fumarate tablets and interventional bronchoscopy improved lung function and reduced symptoms such as shortness of breath and dyspnea. These effects are due to the fact that formoterol fumarate exerts a strong positive effect on bronchial dilation, and it activates adenylate cyclase by acting on β2 receptor in the respiratory tract. The activation of adenylate cyclase increases cellular levels of cyclic adenosine monophosphate, reduces levels of free Ca²⁺, relaxes bronchial smooth muscle, and reduces airway resistance, thereby decreasing clinical symptoms in patients. Interventional bronchoscopy quickly removes tumor tissue in the airway, reduces symptoms of respiratory obstruction, mitigates atelectasis and

Figure 2: Data on survival of patients with malignant tumor
obstructive pneumonia, and improves lung function, thereby significantly relieving central airway stenosis [24, 25].

Ventilation and acid-base balance in the patients were fully assessed through blood gas analysis. The results revealed that all patients had higher pH, PaO₂ and lower PaCO₂ values after treatment, suggesting that formoterol fumarate tablets in combination with interventional bronchoscopy restored levels of blood gas indices in the patients. In addition, a 2-year follow-up of 70 patients with benign tumor showed good curative effect and absence of recurrence. There were 43 survivors (51.19 % survival rate) out of 84 patients with malignant tumor. Therefore, formoterol fumarate tablets and interventional bronchoscopy were effective in the treatment of benign and malignant tumor in central airway. The findings in the present study provide a new direction for the treatment of central airway tumor.

Limitations of the study

There are some limitations in this study that need to be addressed in future research. The study was limited by small sample size. There is need for use of a larger sample size in subsequent studies so as to enhance the acceptability and validity of the present findings. Furthermore, no in-depth study was performed on the complications in patients. Therefore, there is need to study these complications in detail in order to confirm the effectiveness of treatment.

CONCLUSION

The combination of formoterol fumarate tablets and interventional bronchoscopy produces significant curative effect on benign and malignant tumor of the central airway in patients. This treatment improves lung function, reduces shortness of breath, improves blood gas indices, and enhances the survival rate of patients. Therefore, this combination strategy should be subjected to larger clinical trials to validate the findings of this study.

DECLARATIONS

Acknowledgements

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Ethical approval

This study was approved by Guizhou Provincial Health Commission, China (approval no. bgzwkj2021-087).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Dandan Fu and Lina Duan conceived and designed the study, and drafted the manuscript. Chi Zhang, Fengjiao Liu and Xingyi Chen collected, analyzed and interpreted the experimental data. Rong Liu and Zheng Li revised the manuscript for important intellectual content. All authors read and approved the final manuscript for publication.

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