Original Article

Budesonide/glycopyrronium/formoterol fumarate co-suspension metered dose inhaler relieves cough after lobectomy: a randomized controlled study

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Background: Cough after pulmonary resection (CAP) has emerged as a prevalent complication. However, existing treatment protocols for CAP lack standardization. The components of the budesonide/glycopyrronium/formoterol fumarate co-suspension metered dose inhaler (BGF MDI) have been consistently documented for their effectiveness in cough management. Consequently, we initiated this clinical trial to evaluate the efficacy and safety of BGF MDI in mitigating CAP.

Methods: Enrolled participants exhibited no pre-existing cough before undergoing lobectomy. The patients were randomly assigned in a 1:1 ratio to either the BGF MDI group or the Control group. The BGF MDI group received BGF MDI for 14 consecutive days postoperatively; each participant in both groups underwent continuous follow-up for 60 days. Cough severity, duration, and cough-related quality of life were evaluated. The primary endpoints were focused on the occurrence of obvious CAP lasting ≥14 days.

Results: Finally, 51 patients in the BGF MDI group and 52 patients in the Control group were included in the analysis after accounting for dropout. The BGF MDI group demonstrated a reduction in the incidence of obvious CAP lasting ≥14 days (13.7% *vs.* 40.4%). The cough-related quality of life for the BGF MDI group on the 14th and 30th days after surgery was higher. Three participants in the BGF MDI group reported palpitations, with no other complications noted.

Conclusions: BGF MDI has shown efficacy and safety in reducing CAP severity and duration. Using BGF MDI after lobectomy helps to alleviate cough symptoms and speed up postoperative recovery.

Trial Registration: Clinicaltrials.gov. Clinical Trial Registry Number: NCT05472350.

Keywords: Lobectomy; postoperative cough; inhalation therapy; life of quality

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Introduction

Persistent cough after pulmonary resection (CAP), a common complication with an incidence rate of 25%, significantly impacts postoperative quality of life (1,2). Injury to the vagus nerve, gastroesophageal reflux, bronchial morphological changes, mediastinal lymph node resection, different anesthesia methods, surgical resection range are all associated with CAP (3-10). However, there is insufficient clinical research evidence to standardize drug therapy for CAP (11-14).

Previous studies have suggested that the combination of inhaled corticosteroid (ICS) and long-acting β2 adrenergic agonist (LABA) can alleviate symptoms in patients undergoing lung resection (12). Long-acting muscarinic receptor antagonist (LAMA) has also been shown to reduce cough sensitivity and has been confirmed to be effective in alleviating cough caused by various etiologies (15-17). Budesonide/glycopyrronium/formoterol fumarate co-suspension metered dose inhaler (BGF MDI) is an ICS, LABA, and LAMA combination spray. It is formally indicated as maintenance therapy for chronic obstructive pulmonary disease (COPD) (18). Nevertheless, there is limited evidence elucidating the efficacy and safety of BGF MDI treatment for CAP.

In this context, we proposed to conduct a single-center, prospective, open-label, randomized controlled trial to clarify the efficacy and safety of BGF MDI in mitigating CAP and provide evidence for treatment in CAP. We present this article in accordance with the CONSORT reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-905/rc) (19).

Highlight box

Key findings

- Budesonide/glycopyrronium/formoterol fumarate co-suspension metered dose inhaler (BGF MDI) significantly reduces the severity and duration of cough after pulmonary resection (CAP), leading to improved cough-related quality of life.

What is known and what is new?

- Although CAP is a common postoperative symptom, limited research has focused on effective treatment strategies. This study provides new clinical evidence demonstrating that BGF MDI can effectively alleviate CAP, offering a promising therapeutic approach.

What is the implication, and what should change now?

- CAP deserves greater recognition in clinical practice. The findings support the consideration of BGF MDI as a viable treatment option for managing CAP, highlighting the need for further research to refine treatment protocols and optimize patient outcomes.

Methods

Study participants

This prospective, single-center, open-label, randomized controlled trial was approved by The First Affiliated Hospital of Guangzhou Medical University Certified Review Board (No. 2021-190; Date: 31 December 2021). The study protocol was registered in the Registry of Clinical Trials (registration number, NCT05472350; registration date: 31 December 2021). Written informed consent was provided by all the participants. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments (20).

The inclusion criteria were as follows: (I) patients are voluntary participants and willing to adhere to the study protocol, understand and comply with required assessments, follow the follow-up plan, and provide written informed consent; (II) patients scheduled for video-assisted lobectomy plus systematic lymph node dissection; (III) absence of cough in the month preceding surgery; (IV) aged between 18 and 70 years with preoperative cardiopulmonary function sufficient to tolerate the surgery. The exclusion criteria were as follows: (I) patients who had participated in other interventional clinical studies within the 90 days prior to enrollment; (II) pregnant or lactating women; (III) patients with significant preoperative cough (as it may affect the assessment of drug efficacy); (IV) history of alcohol abuse, substance abuse, or a psychiatric disorder, as well as traits of hostility, adverse motivation, paranoia, or other emotional or intellectual issues that may affect the validity of informed consent and participation in the study; (V) severe congestive heart failure or preexisting heart-related conditions prior to surgery, since LABA and LAMA may potentially worsen heart failure (21,22); (VI) poorly controlled diabetes before surgery; (VII) severe preoperative hepatic or renal impairment; (VIII) patients who used an angiotensin-converting enzyme inhibitor (ACEI) within one month before surgery, because taking ACEI may induce a dry cough, affecting cough assessment (23); (IX) severe narrow-angle glaucoma, severe benign prostatic hyperplasia, or severe bladder neck obstruction in the month preceding surgery, because LAMA may contract smooth muscles of organs and exacerbate these conditions; (X) patients who used ICS, LABA, or LAMA within one month before surgery; (XI) situations where study personnel determine

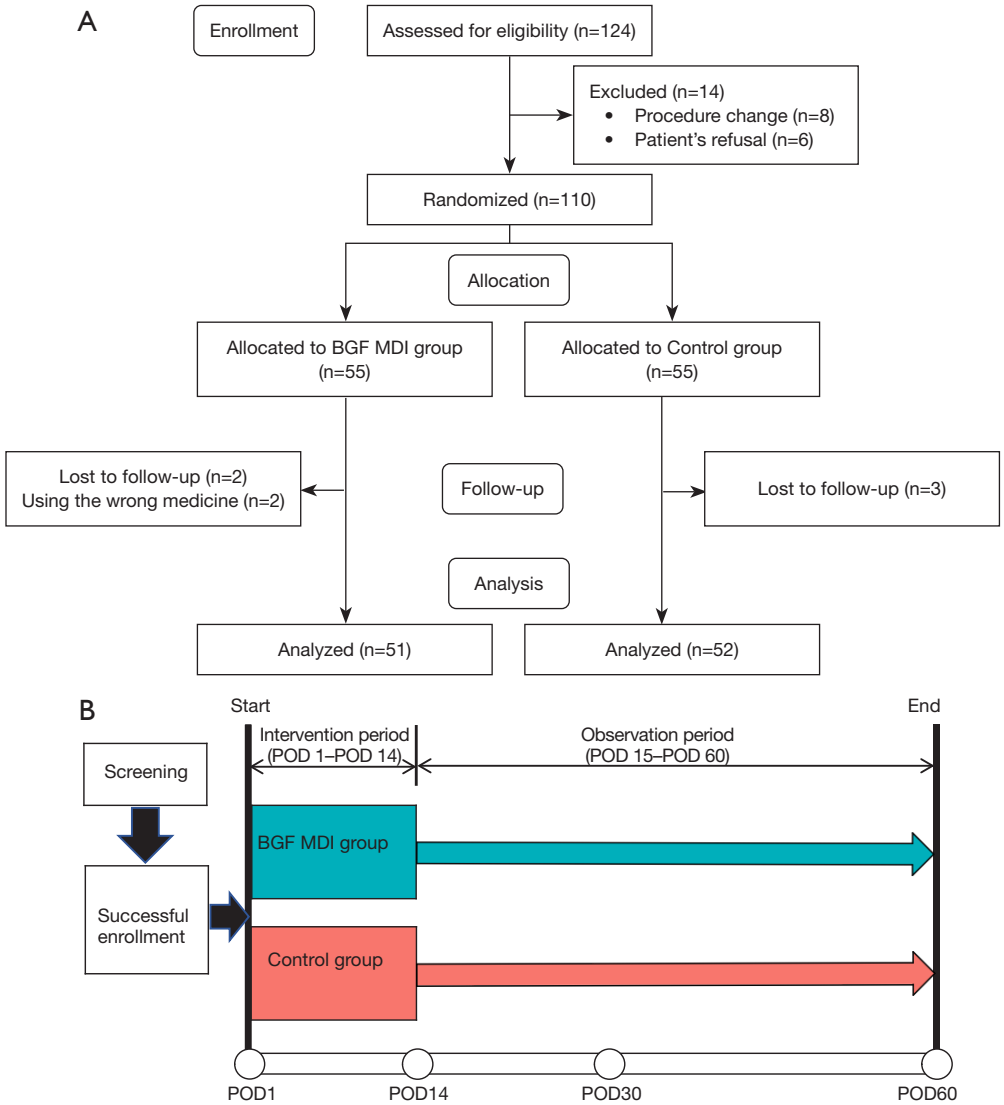

Figure 1 Study flowchart (A) and summary of study design (B). BGF MDI, budesonide/glycopyrronium/formoterol co-suspension metered dose inhaler; POD, postoperative day.

that inclusion in the study is not appropriate.

Surgery

All participants underwent lobectomy and mediastinal lymph node dissection via uniportal three-dimensional (3D) thoracoscopy. Double-lumen endotracheal intubation was used for all participants. For those who had surgery on the left side, groups 4, 5, 6, 7, and 9 lymph nodes were dissected, whereas for those who had surgery on the right side, groups 2, 4, 7, and 9 were dissected. Special care was taken to protect the nerves surrounding the lymph nodes during the dissection process.

Intervention

Patients in the BGF MDI group received two sprays of BGF MDI twice daily for a consecutive period of 14 days starting from the first day after surgery. Before using BGF MDI, patients underwent guidance from a specialized pulmonary rehabilitation nurse to ensure the correct administration of the inhaler (*Figure 1*).

All participants postoperatively received intravenous antibiotic therapy for 48 hours after surgery to prevent

infection. Since gastroesophageal reflux has been reported as a cause of CAP, oral anti-reflux medications may mitigate postoperative CAP (4). Therefore, all patients received oral omeprazole to reduce the impact of gastroesophageal reflux on CAP. All patients also received Ambroxol nebulization combined with mechanical assistance for sputum expectoration. Medications commonly used for CAP alleviation but lacking clinical evidence for efficacy in CAP, such as montelukast, loratadine, dihydrocodeine, levomethorphan, and compound methoxyphenamine capsules, were prohibited in this study.

Randomization

In our open-label randomized controlled trial, we used block randomization to ensure balanced group sizes across the study arms. The randomization sequence was generated using a computerized random number generator. Although the study was open-label, allocation concealment was maintained using sealed, opaque envelopes to prevent foreknowledge of the group assignments during the randomization process. After enrolment, participants were assigned to their respective groups based on the concealed allocation sequence.

Cough measurement

Cough was measured by cough visual analog scale (VAS) within 60 days after surgery and the Mandarin Chinese version of the Leicester Cough Questionnaire (LCQ-MC) on the 14th, 30th, and 60th day after surgery.

The cough VAS is widely used in cough assessment (24). It is a linear scoring method, with a scale of 0–100 mm. Score ranges from ≤30 for mild cough, >30 and ≤60 for moderate cough, and >60 for severe cough. Moderate and severe cough are considered an obvious cough. The duration of coughing was only calculated when the cough VAS was >10, as cough with a VAS ≤10 can be almost negligible.

The LCQ-MC is a useful tool to evaluate CAP (25). The LCQ-MC is divided into three dimensions: physical, psychological, and social. There are a total of 19 questions, and each question has seven options (grades 1–7, the higher the score is, the lighter the cough). The minimal clinically important difference (MCID) of LCQ-MC is 1.3 (25).

Study endpoint

The primary endpoint was the incidence of obvious CAP lasting ≥14 days. We believe that obvious and prolonged cough has the greatest impact on patients and has the most clinical significance. The primary safety endpoint was the incidence of adverse reactions. The secondary endpoints included onset of cough, duration of cough, the incidence of obvious cough lasting ≥30 days, the incidence of obvious cough lasting ≥60 days; cough precipitating factor, LCQ-MC 14 days after surgery, LCQ-MC 30 days after surgery, LCQ-MC 60 days after surgery, cough VAS, hospital stay, duration of drainage, and duration of anesthesia.

Statistical analysis

The incidence of persistent CAP, without considering the surgical procedure, has been reported at approximately 25% (2). The persistent CAP incidence is expected to be higher in cases of lobectomy combined with mediastinal lymph node dissection (9). Based on literature and clinical experience, assuming a 30% persistent CAP incidence after lobectomy with mediastinal lymph node dissection, it can be understood that the effective prevention rate of persistent CAP in the Control group is 1 – 30% =70%. Reports suggest that ICS plus LABA has an effective prevention rate of 90% for persistent CAP (12). Assuming that BGF MDI has an effective prevention rate of 75% for persistent CAP, the effective prevention rate for the BGF MDI group against persistent CAP is calculated as 92.5%. Considering a power of 0.8, α set at 0.025, and utilizing PASS software (NCSS LLC, East Kaysville, UT, USA) for calculation, the determined sample size was 88. Accounting for a 20% dropout rate, the total sample size was set at 110.

The normality assumption for continuous variables was assessed using a test-based procedure. Normally distributed data were shown as the mean ± SD, and independent samples *t*-tests were used to compare groups. Non-normally distributed data were shown as the median [interquartile range (IQR)] relative frequencies, and Mann-Whitney *U* test was used to compare groups. Categorical variables were presented as frequencies and percentages and assessed using the Chi-squared test or Fisher's exact test. Choosing between the Chi-squared test and Fisher's exact test is typically based on the expected cell counts in the contingency table. The Chi-squared test is generally used when all expected cell counts are five or more, whereas Fisher's exact test is preferred when there are small sample sizes or when any expected cell count is less than five. The cough VAS curve at each day was plotted by means [95% confidence interval (95% CI)] and compared between the

two groups using the Mann-Whitney *U* test. Missing data were handled by imputation. LCQ-MC on the 14th, 30th, and 60th days after surgery were compared between the two groups using Mann-Whitney *U* test. All reported P values were two-sided and those under 0.05 were considered statistically significant. Statistical analyses were performed using R 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS 26.0 software (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

We initially screened 124 patients, with 14 excluded from the screening period. Eight patients withdrew from the study due to a surgical procedure other than lobectomy with lymph node dissection, and six patients withdrew due to refusal to sign the informed consent. Among the remaining 110 patients, 55 were allocated to the BGF MDI group, and 55 were assigned to the Control group. In the BGF MDI group, two individuals withdrew due to protocol violations during medication use, and two were lost to follow-up. In the Control group, three individuals were lost to follow-up. Ultimately, data from 51 patients in the BGF MDI group and 52 patients in the Control group were included in the analysis. The study flowchart and summary of study design are presented in *Figure 1*.

In terms of the baseline, patient demographics, clinical characteristics, and operative and immediate post-operative procedures were similar between groups (*Table 1*).

Efficacy and safety endpoints

The BGF MDI group showed a significant reduction in the incidence of obvious cough ≥14 days (13.7% *vs.* 40.4%, P=0.002) and ≥30 days (5.9% *vs.* 21.2%, P=0.02). The number of participants experiencing cough for ≥60 days in the BGF MDI group was significantly lower than that in the Control group (23.5% *vs.* 48.1%, P=0.007). The severity of CAP in the BGF MDI group was significantly lower than in the Control group on the 3rd (P<0.001), 14th (P=0.02), and 60th (P=0.02) days. Three participants in the BGF MDI group experienced palpitations, but no other complications were noted (*Table 2*). To assess the robustness of our findings, a sensitivity analysis was performed. The results remained consistent with the primary analysis (Tables S1-S3).

Cough characteristics

In both BGF MDI group and Control group, CAP severity reached its peak at around two weeks postoperatively and gradually decreased thereafter. CAP is characterized by mild to moderate cough, but its duration can be prolonged (*Figure 2*). Itchy throat and speaking are common precipitating factors for CAP. No circadian rhythm of CAP was observed in this study (*Table 3*).

LCQ-MC

Bar charts of LCQ-MC of the two groups on the 14th, 30th, and 60th day after surgery are displayed in *Figure 3*. On the 14th day, the BGF MDI group had a significantly

Table 1 Characteristics of patients in the BGF MDI group and Control group

Characteristics	BGF MDI (n=51)	Control (n=52)	P value
Gender			0.61
Male	21 (41.18)	24 (46.15)	
Female	30 (58.82)	28 (53.85)	
Age (years)	58 [51–65]	57.00 [49–63]	0.56
BMI (kg/m^2)	22.03 [20.70–24.22]	22.60 [20.81–25.59]	0.46
Hypertension			0.75
Yes	8 (15.69)	7 (13.46)	
No	43 (84.31)	45 (86.54)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	BGF MDI (n=51)	Control (n=52)	P value
Diabetes			0.09
Yes	2 (3.92)	7 (13.46)	
No	49 (96.08)	45 (86.54)	
COPD			0.97
Yes	1 (1.96)	1 (1.92)	
No	50 (98.04)	51 (98.08)	
Asthma			>0.99
Yes	0 (0.00)	0 (0.00)	
No	51 (100.00)	52 (100.00)	
Smoking history			0.42
Yes	6 (11.76)	9 (17.31)	
No	45 (88.24)	43 (82.69)	
Pack-years	30 [7.5–30]	27.5 [21.88–32.5]	0.82
Position			0.08
Left upper lobe	11 (21.57)	11 (21.15)	
Left lower lobe	8 (15.69)	8 (15.38)	
Right upper lobe	16 (31.37)	8 (15.38)	
Right middle lobe	12 (23.53)	11 (21.15)	
Right lower lobe	4 (7.84)	14 (26.92)	
Lung function			
FEV1%	102.30 [89.81–107.73]	101.20 [90.42–107.32]	0.73
FVC%	105.05 [93.97–114.02]	103.61 [98.15–110.70]	0.86
FEV1/FVC%	97.33 [89.92–101.14]	96.52 [88.36–104.83]	0.93
Double lumen endotracheal intubation	51 (100.00)	52 (100.00)	>0.99
Minimally invasive surgery	51 (100.00)	52 (100.00)	>0.99
Neoadjuvant therapy			0.72
Yes	3 (5.88)	4 (7.69)	
No	48 (94.12)	48 (92.31)	
Adjuvant therapy			0.18
Yes	5 (9.80)	10 (19.23)	
No	46 (90.20)	42 (80.77)	
Anesthesia time (minute)	180 [165–210]	196 [160–225]	0.97
Hospital stay (days)	7 [5–10]	7 [5–10]	0.83
Drainage time (days)	3 [2–3]	3 [2–3]	0.72

Data are presented as n (%) or median [interquartile range]. BMI, body mass index; BGF MDI, budesonide/glycopyrronium/formoterol fumarate co-suspension metered dose inhaler; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2 Efficacy and safety

Outcome	BGF MDI (n=51)	Control (n=52)	P value
Cough duration			
Obvious cough ≥14 days	7 (13.7)	21 (40.4)	0.002
Obvious cough ≥30 days	3 (5.9)	11 (21.2)	0.02
Obvious cough ≥60 days	0 (0.0)	1 (1.9)	>0.99
Cough ≥14 days	43 (84.3)	50 (96.2)	0.09
Cough ≥30 days	35 (68.2)	45 (86.5)	0.03
Cough ≥60 days	12 (23.5)	25 (48.1)	0.007
Cough severity (VAS)			
Day 1	0 [0–5]	0 [0–10]	>0.99
Day 3	4 [0–20]	20 [0–30]	<0.001
Day 7	20 [12–30]	30 [20–40]	0.06
Day 14	28 [16–30]	40 [30–49.5]	0.02
Day 30	20 [10–30]	30 [20–35]	0.06
Day 60	2 [0–10]	10 [8–25]	0.02
Side effects			
Oral candidiasis	0 (0.0)	0 (0.0)	>0.99
Pneumonia	0 (0.0)	0 (0.0)	>0.99
Insomnia	0 (0.0)	0 (0.0)	>0.99
Palpitation	3 (5.9)	0 (0.0)	0.23
Dysphonia	0 (0.0)	0 (0.0)	>0.99

Data are presented as n (%) or median [interquartile range]. BGF MDI, budesonide/glycopyrronium/formoterol fumarate co-suspension metered dose inhaler; VAS, visual analog scale.

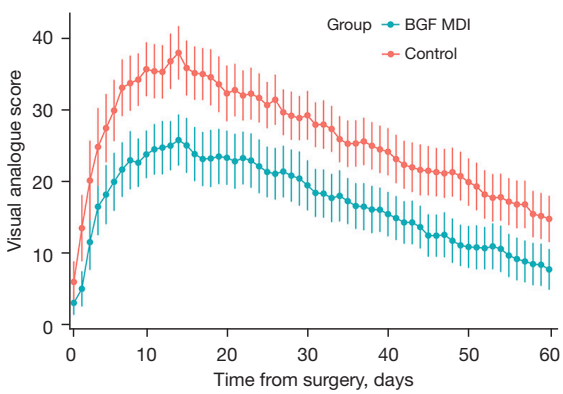

Figure 2 Cough VAS curve. Changes in cough VAS over postoperative 60 days. BGF MDI, budesonide/glycopyrronium/formoterol co-suspension metered dose inhaler; VAS, visual analogue scale.

higher total score (15.67±1.96 *vs.* 14.33±2.89, P=0.005), physical score (5.06±0.69 *vs.* 4.62±0.86, P=0.005), psychological score (5.33±0.67 *vs.* 4.82±1.11, P=0.01), and social score (5.28±0.83 *vs.* 4.89±1.09, P=0.04) for LCQ-MC compared to the Control group. Similarly, on the 30th day, the BGF MDI group still showed a significantly higher total score (16.46±2.25 *vs.* 15.25±2.76, P=0.01), physical score (5.37±0.78 *vs.* 4.96±0.93, P=0.02), psychological score (5.57±0.8 *vs.* 5.13±1.01, P=0.02), and social score (5.52±0.87 *vs.* 5.16±0.96, P=0.046). On the 14th day, the total (15.67±1.96 *vs.* 14.33±2.89, P=0.005) scores of the two groups were greater than that of MCID. In the LCQ-MC assessment on the 60th day, a significantly higher score was observed only in the physiological aspect (5.94±0.79 *vs.* 5.63±0.97, P=0.02), whereas the total score (17.64±2.04

Table 3 Characteristics of cough

Outcome	BGF MDI (n=51)	Control (n=52)	P value
Precipitating factor			
Itchy throat	23 (45.1)	28 (53.8)	0.38
Speaking	17 (33.3)	24 (46.2)	0.18
Cold air	6 (11.8)	8 (15.4)	0.59
Exercise	8 (15.7)	10 (19.2)	0.64
Peculiar smell	6 (11.8)	5 (9.6)	0.72
No obvious cause	10 (19.6)	8 (15.4)	0.57
Circadian rhythm			
Nighttime	19 (37.3)	18 (34.6)	0.78
Daytime	22 (43.1)	25 (48.1)	0.62
Both	15 (29.4)	12 (23.1)	0.47

Data are presented as n (%). BGF MDI, budesonide/glycopyrronium/formoterol fumarate co-suspension metered dose inhaler.

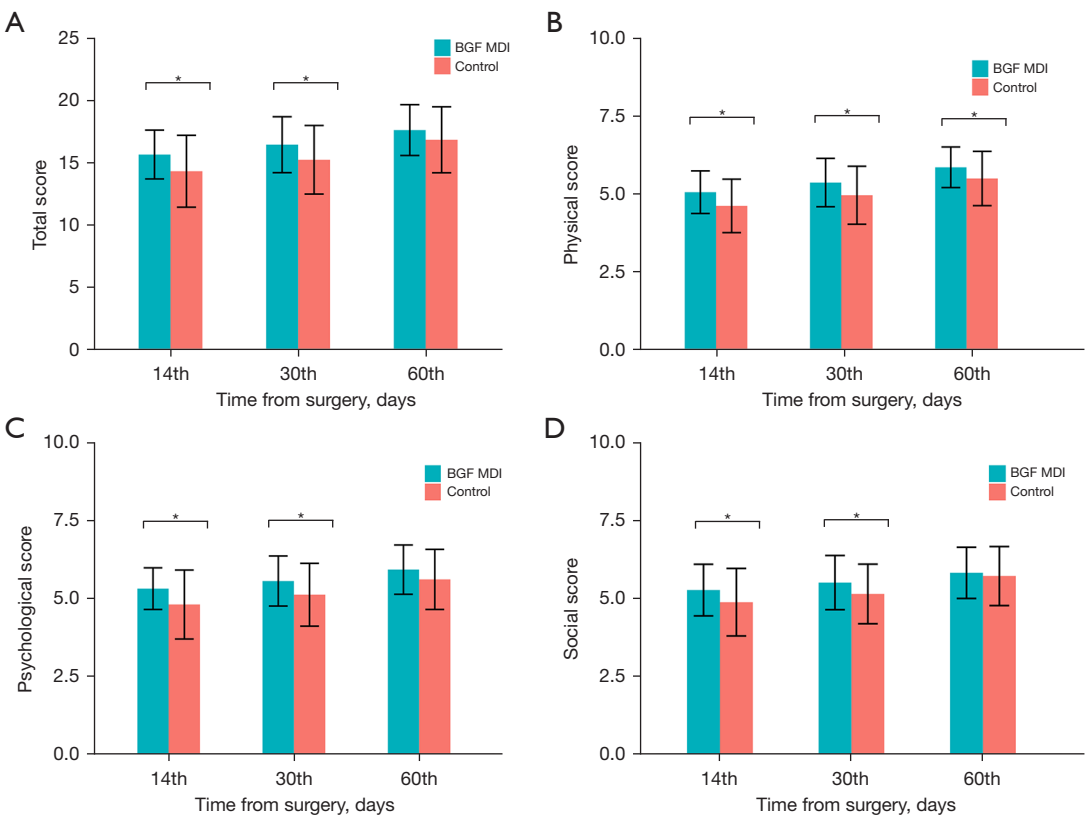

Figure 3 LCQ-MC at 14, 30, and 60 days after surgery. (A) Total score of LCQ-MC. (B) Physical score of LCQ-MC. (C) Psychological score of LCQ-MC. (D) Social score of LCQ-MC. *, P<0.05. BGF MDI, budesonide/glycopyrronium/formoterol co-suspension metered dose inhaler; LCQ-MC, Mandarin Chinese version of the Leicester Cough Questionnaire.

vs. 16.86±2.65, P=0.12), psychological score (5.94±0.79 *vs.* 5.63±0.97, P=0.13), and social score (5.84±0.82 *vs.* 5.74±0.95, P=0.74) showed no significant differences (*Figure 3*).

Discussion

This single-center, prospective, open-label, randomized controlled trial aimed to assess the efficacy and safety of BGF MDI in mitigating CAP. We enrolled patients who had undergone lobectomy with lymph node dissection and showed no preoperative cough. The treatment protocol was rigorously standardized, and known confounding factors were meticulously controlled. This study revealed that BGF MDI demonstrated a significant capacity to alleviate the severity and shorten the duration of CAP. It contributes valuable insights to CAP management, shedding light on the potential of BGF MDI as a promising therapeutic option for accelerating postoperative rehabilitation in patients undergoing pulmonary surgery.

To alleviate CAP, Miyamoto *et al.* (26) found that suplatast tosilate helped to control chronic dry cough after lung cancer surgery. In a study conducted by Sawada *et al.* (12), patients undergoing lung resection were administered ICS plus LABA, resulting in a reduction in cough severity after two weeks of treatment. However, these studies had small sample sizes and short observation periods, thus providing limited evidence.

BGF MDI adds LAMA to the ICS plus LABA combination, which is considered a drug that can reduce cough sensitivity (15-17). Its antitussive effect is theoretically expected to be more significant than that of the dual therapy with ICS and LABA. However, based on the published literature, a direct comparison of the efficacy between dual and triple therapies on CAP is not yet possible. In this study, BGF MDI mitigated cough severity and shortened the duration of CAP, significantly improving early postoperative quality of life. Besides the direct effects of BGF MDI in reducing airway inflammation and relieving bronchospasm, the timing of administration is also crucial. Previous research underscores the efficacy of preventing chronic cough and avoiding overtreatment (27,28). Although addressing chronic cough remains essential, the primary focus should be on preventing its development. Postoperative acute cough is an independent risk factor for chronic cough (9). Effectively suppressing cough in the acute stage has the potential to reduce the incidence, duration, and intensity of chronic cough. The positive results of this study may contribute to the validity of BGF MDI administration on the first day postoperatively, intervening early to address CAP.

BGF MDI exhibits favorable tolerability in both healthy individuals and patients with COPD (29-31). The observed adverse reactions are consistent with those associated with its individual components and are generally mild, which is typical for a local inhalation formulation, resulting in minimal systemic effects. Localized adverse reaction commonly includes respiratory difficulties and hoarseness. Previous research has indicated a low likelihood of developing hoarseness when utilizing ICS plus LABA to manage CAP, and such symptoms tend to resolve upon cessation of treatment (12). In this study, palpitations were observed in three patients; however, these promptly disappeared after discontinuing the BGF MDI treatment. This observation underscores the safety and controllability of BGF MDI use, indicating minimal adverse reaction when employed correctly.

There are several limitations in this study. First, despite our efforts to control for confounding variables, it is important to acknowledge that the placebo and open-label design can introduce bias, especially in studies involving patient-reported details. To mitigate this limitation, employing blind methods or incorporating a placebo group is necessary. Secondly, another limitation arises from our inability to differentiate which component within BGF MDI is most effective in alleviating CAP in this study. Future investigations could focus on individual treatments with ICS, LABA, or LAMA to elucidate the therapeutic effects of each component.

Conclusions

This study indicates that the perioperative use of BGF MDI relieves both the severity and duration of CAP and improves cough-related quality of life. Notably, BGF MDI exhibits a favorable safety profile, characterized by minimal adverse effects.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-905/rc

Trial Protocol: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-905/tp

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-905/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-905/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This trial was approved by The First Affiliated Hospital of Guangzhou Medical University Certified Review Board (No. 2021-190; Date: 31 December 2021). Written informed consent was provided by all the participants. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

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