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Mucosolvan serves to optimize perioperative airway management for NSCLC patients in fast track surgery: a randomized placebo controlled study

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Abstract. – OBJECTIVE: This study is conducted to investigate whether mucosolvan may offer therapy optimization initiatives for airway perioperative management of patients with non-small cell lung cancer (NSCLC) in fast track surgery (FTS).

PATIENTS AND METHODS: The patients in FTS were treated with and without aerosol (90 mg/day) of mucosolvan in combination of intravenous administration of the agent (180 mg/day) for 8 consecutive days. Postoperative complications and length of time of hospital stay were examined in the patients treated with and without mucosolvan.

RESULTS: Prevalence rate for the overall postoperative complication was significantly decreased in the mucosolvan-treated patients as compared to the untreated ones ($p < 0.05$). In further analysis, an appearance of postoperative pulmonary complication was reduced in the treated patients as well ($p < 0.05$). There was no statistical difference in a morbidity rate of postoperative cardiac complications between these two groups. Furthermore, treatment with mucosolvan resulted in significantly decreasing length of time of hospital stay as compared to the untreated patients ($p < 0.05$), indicating that this agent may facilitate early recovery of the patients in FTS after major surgical approaches.

CONCLUSIONS: Mucosolvan optimizes the perioperative airway management for NSCLC patients in FTS through reducing postoperative complications and shortening time of hospital stay.

Key Words:
Mucosolvan, FTS, NSCLC, Perioperative airway management, Postoperative complication and hospital stay.

Introduction

Non-small-cell lung cancer (NSCLC) is the most common type of lung cancer and is primarily treated by surgical resection with curative intent since the cancer is relatively insensitive to chemotherapy[1-3]. The respiratory system is invariably affected during and after thoracic surgery. Since the elderly people with lung cancer often have other lung diseases such as chronic obstructive pulmonary disease, this may result in the development of postoperative cardiopulmonary complications with a low success rate for the surgical treatment[4,5].

The term fast track surgery (FTS) refers to a combination of findings from studies of anaesthetics, surgery and perioperative care for a certain medical indication[6,7]. FTS is a procedure specific, evidence based and inter-professionally optimized course of therapy that includes epidural anaesthesia, minimally invasive techniques, and aggressive postoperative rehabilitation[8-10]. Since FTS combines various techniques used in the care of patients undergoing elective operations, the combination of these approaches reduces the perioperative stress response and complications and, therefore, greatly shortens the time required for full recovery.

Mucosolvan is a clinically proven systemically active mucolytic agent with less cost and works in a unique way to stimulate surfactant, which helps lubricate the airways[11]. Although effects of mucosolvan on the patients with respiratory diseases have been examined in its clinical significance[12], it is still lacking in the understanding of the agent as therapy optimization initiative contributing to airway perioperative management for the patients in a FTS program.

In order to increase a success rate of surgical treatment and facilitate early recovery after major surgical procedures, an effect of mucosolvan on the perioperative airway management was investigated with its clinical interests on the therapy optimization initiative observed in NSCLC patients received FTS.

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Patients and Methods

Patients and Inclusion Criteria

We recruited 140 NSCLC patients required surgical excision of the lung cancer in the period from 2008/01-2013/05. These patients included 98 males and 42 females aged 44-76 years (median, 67.3 ± 9.60 years) for the study. Major inclusion criteria were (1) Preoperative prediction of lung function including predicted postoperative FEV_1 (ppo FEV_1) in a absolute value > 1.5 L, predicted postoperative ppoFEV_1 in one second < 30%, predicted postoperative CO diffusion capacity of the lung (ppoDLCO) < 30%, maximum capacity for oxygen transport during incremental exercise (VO2 peak) < 10 ml/kg/min; (2) No serious cardiopulmonary complications and other organ dysfunction; 3) Well-controlled hypertension and diabetes mellitus; (4) Normal limb movements; (5) No radiotherapy and chemotherapy available prior to surgery.

Experimental design for data values of subjects was under statistical consideration and had to satisfy the conditions: (1) NSCLC diagnosed by pathologic examination; (2) TNM stage confirmed according to the International Association for the Study of Lung Cancer (IASLC)[13]; (3) There were no statistical differences in gender, age, the results of lung function tests, time and types (hemi-pulmonectomy and lobectomy) of surgical procedure, and subpopulation distribution of the patients at same TNM stage between the experiential groups (Figure 1). Furthermore, same type of anaesthesia was applied to the individual surgeries of the patients.

The study has been approved by the Ethics Committee of East Hospital of Tongji University in September 2007; the Ethics Committee also approved the related screening, treatment, and data collection from these patients based on the experimental design and analysis of clinical outcome. All subjects signed written informed consent forms for this study.

Preoperative Education and Preparation

Before FTS, patient education would be an integral part of medical management. It implied thorough explanations and realistic information about the medical and surgical procedures. The education may gain patient cooperation to reduce the need for pain relief and anxiety due to psychological block in perioperative medical care. It would place the patient in the proper position of an important partner in the medical act.

Patients received pre-surgical tests of respiratory function and trainings on exercise of breathing movements including muscular movements of diaphragm and intercostal muscles that not on-

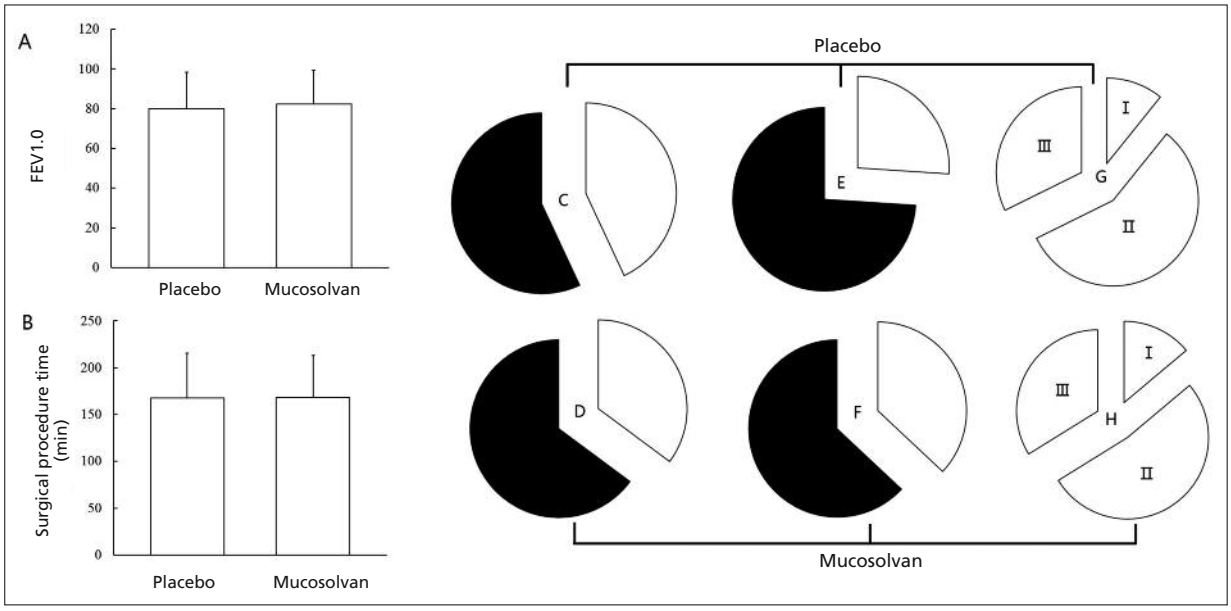

Figure 1. Clinical features of NSCLC patient in FTS. FEV1 test ***(A)*** prior to surgery and measurements of surgical procedure time ***(B)*** for the patients receiving FTS were performed in the presence and absence (*placebo*) of mucosolvan. The results are expressed as the Mean ± SD. Population distributions (black) for the patients received right pneumectomy ***(C, D)*** and a right upper lobectomy ***(E, F)*** were calculated with a percentage in each group. The subpopulation distribution (*black*) for the patients at the indicated stages was shown ***(G, H)***. A *p*-value was > 0.05 in all results compared between these two groups.

ly enables the passage of air to and from the lungs but also expands lungs. The patients proceeded with the trainings on breath-hold time, productive cough and maximal expiration and inspiration in case of occurrence of postoperative atelectasis.

Liquid diet used for the patient was typically associated with medical procedures. It was controlled in an amount of 300-500 ml at 21:00 PM of the day before the surgery and carbohydrate drinks taken at a 2-hour prior to the surgery, respectively. Antibiotics including cefuroxime were also applied to the patients in advance.

Therapeutic Approaches

140 NSCLC patients were randomly assigned to two groups of 70 patients each. The patients in a FTS program were treated with aerosol of mucosolvan (30 mg dissolved in 20 ml physiological saline, three times a day) and an intravenous administration of the agent (90 mg, twice a day) for 8 consecutive days. The patients in FTS did not receive mucosolvan treatment as a placebo. Use of mucosolvan started on the 3rd day before the surgery and ended on the 5th day after the surgery.

Minimally invasive approach was applied to patients under systemic analgesia with epidural analgesia at 37°C in the entire procedure. Briefly, resection of lung cancer was performed using video-assisted lobectomy and video-assisted mini-thoracotomy. During the surgery, a thorascope (small video camera) and surgical instruments were inserted into the incisions. The surgical approach was guided by the images of the operative area transmitted from the thorascope while performing the surgical treatment. The images were projected onto a computer monitor that was positioned next to the patient. The tumor or affected tissue was removed from the lung through the small incisions. Before completing the procedure, one or two drains remained in place after the surgery to remove excess fluid and air from around the lung, whereas the intercostal nerves on the side of the incision between the ribs were frozen to relieve pain after the surgery.

Postoperative Measurement and Observation

Patient's pain in postoperative care was relieved by a method of patient-controlled epidural analgesia. A mixture of medications containing 3-5 mg morphine, 100-150 mg bupivacaine and 5-10 mg droperidol in 100 ml physiological saline was delivered into the spinal fluid area at a rate of 2.0 ml/hour within 48 hours after the surgery. It was not necessary for the patients to be admitted to ICU if no cardiopulmonary complications occurred. The drainage tubes were removed within 24 hours if the amount of draining fluid from the chest cavity was decreased. An amount of intravenous infusion was controlled at 500-1000 ml/day with cefuroxime used for prevention of infection.

On the day of the surgery the patients were encouraged to sit up on the bed 1-2 times with limbs movement, especially for lower limbs movement. Next day the patients requested an increased activity of the movement on the bed and got off it 1-2 times when the drainage tube was taken out from the patients' chest. On day 2, the patients required to gradually increase ambulation. A supplement to patient's diet was available with 300ml carbohydrate drink taken at a 2-hour after the surgery if no nausea and vomiting occurred. Liquid diet was scheduled at a 4-hour after the surgery and followed up with a normal meal on the next day.

Postoperative pulmonary complications including respiratory failure supported by a mechanical ventilator over a 48-hour, atelectasis, lung infection, prolonged air leaks (> 7 days) required the presence of drainage tubes in the chest after the lung surgery and pleural effusion on the 2nd day after the drainage tubes removed were confirmed by clinical examinations of a chest X-ray, lung CT scan, white blood cell count and C-reactive protein (a marker of inflammation found in blood). Cardiac complications such as arrhythmias and myocardial infarction were diagnosed by electrocardiogram. Other observations including surgical technique-related wound infection, mechanical ventilation time, changes in lung function tests before and after the operation, time of hospital stay were also performed in the treated patients.

Statistical Analysis

Values were expressed as a percentage of distribution data from the investigated patients and Mean ± Standard Deviation (SD) on some of the results, respectively. Statistical analysis was performed using Statistical Package for the Social Science (SPSS, version 13.0, Chicago, IL, USA). Comparisons from groups with individual measurements were performed by Student's paired *t* test in between of two groups. The Chi-square test (χ^2) was conducted to analyze the signifi-

cance of a parameter within groups. A p value of < 0.05 was considered significant.

Results

Clinical features of NSCLC patients in FTS

In order to validate an effect of mucosolvan on perioperative airway management, clinical features of NSCLC patients in a FTS program were examined and compared in population distribution models to estimate the accuracy of results. The data are shown in Figure 1. Examination of FEV_1 prior to surgery and surgical procedure time (min) were performed in the patients requiring mucosolvan treatment (Figure 1A, B). The values for FEV_1 test (%) and the procedure time (min) were shown as 79.90±18.53 and 167.58±48.07 in the placebo-controlled patients; 82.27±16.91 and 168.34±44.84 in the mucosolvan-treated patients. The results are expressed as the Mean ± SD. There were no statistical differences in the observations between these two groups (both $p > 0.05$).

The number of NSCLC patients received either right pneumectomy or a right upper lobectomy was examined and calculated with a percentage in each group (Figure 1 C-F). The results showed that 56.92% and 64.62% of patients received right pneumectomy and 73.85% and 63.08% of the patients applied to a right upper lobectomy in the presence and absence of mucosolvan, respectively. In contrast, there was similar population density in two groups with no statistical differences seen in the given simple model (χ^2 test, both $p > 0.05$).

In terms of the classification and degrees of malignant tumors, subpopulations for the individuals at TNM stage I-III were examined in NSCLC patients and compared at the same stage between these two groups (Figure 1 G, H). The results showed that there were 14% and 11%, 52% and 57%, and 34% and 32% of the patients treated with and without mucosolvan in each of stage I-III, respectively. There was similar subpopulation distribution detected in the same stage between these two groups of the patients (All $p > 0.05$).

Prevalence of Postoperative Complication in NSCLC Patients

Effect of mucosolvan on NSCLC patients in FTS was assessed in two groups of 70 patients each. Occurrence rate of postoperative complications was observed in both groups and the results are shown in Figure 2. The population for an overall postoperative complication was calculated with a percentage in each group. An effective treatment for decreasing occurrence of the complication was shown as 13% and 27% in the patients treated with and without mucosolvan, which was about a 2-fold lower than that a placebo (Figure 2 A, B). There was a significantly statistical difference in population distribution of the patients with the complication between these two groups (^{2} test, $p < 0.05$).

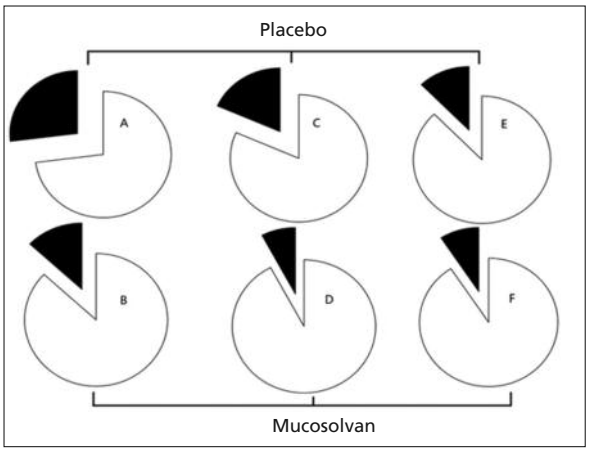

Figure 2. Effect of mucosolvan on postoperative complication. Effect of mucosolvan on perioperative airway management of NSCLC patients in FTS was assessed in two groups of 70 patients each. Population distribution (*black*) for an overall complication ***(A, B)***, pulmonary ***(C, D)*** and cardiac complications ***(E, F)*** of the patients was examined in the presence and absence (*placebo*) of mucosolvan, respectively. The Morbidity rate of the complications was expressed with a percentage in each group. A χ^2 test showed a p-value of < 0.05 between either A vs B or C vs D groups.

In further understanding of the general postoperative complication, pulmonary complications including infection, atelectasis, prolonged air leaks and pleural effusion (empyema) were investigated in NSCLC patients received FTS. A morbidity rate of the pulmonary complication in a general population was calculated with a percentage in each group. The results showed that 8% and 19% of the patients treated with and without mucosolvan suffered from the complication, respectively (Figure 2 C, D). In contrast, the population distribution in the mucosolvan-treated patients was a 2.4-fold lower than the placebo-controlled ones with a statistically significant difference observed in occurrence of the pulmonary complication between these two groups (χ^2 test, $p < 0.05$).

In association with observation of the pulmonary complication, occurrence rate for postoperative cardiac complication including arrhyth-

mias and myocardial infarction was investigated in NSCLC patients received FTS. A morbidity rate for a general cardiac complication was calculated with a percentage in each group and shown as 9.0% and 12.0% in the patients treated with and without mucosolvan, respectively (Figure 2 E, F). There was a similar population distribution in appearance of the cardiac complication between these two groups ($p > 0.05$).

Length of Time for NSCLC Patient Staying in Hospital

Length of time (day) of hospital stay for NSCLC patients in FTS was examined in the presence and absence of mucosolvan, and the results are shown in Figure 3. Average lengths of time for the hospital stay were 7.77±2.52 and 11.62±3.99 in the patients treated with and without mucosolvan, respectively. A time-period for the hospital stay in the mucosolvan-treated patients significantly shortened with a median value of a 4-day cut down as compared to the placebo-controlled ones. In contrast, there was statistically significant difference observed in the decreasing time of hospital stay in the patients received FTS between these two groups ($p < 0.05$).

Discussion

To validate the effect of mucosolvan as optimization therapy initiatives on airway perioperative management for NSCLC patients in a FTS program, the lung function test prior to surgery and the surgical approaches-related factors were assessed in a sampling frame of same population. Our data showed that the FEV_1 values were similar in these two groups of the patients enrolled to be treated with and without mucosolvan, whereas time for surgical approaches was almost same in the groups as well. Since the success rate of anatomical pulmonary resection for primary bronchial cancer varies with the type of surgery being performed and the quality of the lung cancer staging[14], the sampling distributions for the patients received either lobectomy or hemi-pulmonectomy were examined in the distinct subpopulations at the same cancer staging with the reason which an overall population is heterogeneous[15]. The results showed that there were similar sample sizes with no statistical difference in the subpopulations between these two groups, indicating that an objective effect of mucosolvan on the investigated patients was not influenced by the staging process and individual types of the surgical approaches in the distribution of the statistic after the tumor was surgically removed.

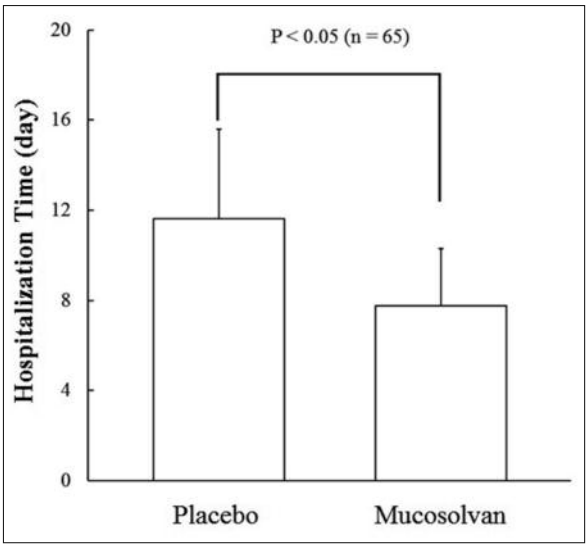

Figure 3. Body weight loss and survival rate in DSS-induced acute IBD mice. Treatment with anti-IL-6 neutralizing antibodies led to more severe symptom of IBD (n=20).

In this randomized placebo-controlled study, one of the major observations was performed through investigating the effect of mucosolvan applied for perioperative airway management of NSCLC patients in FTS[16]. Our results showed that mucosolvan combined FTS markedly lowered the occurrence for a general postoperative complication of the patients in the pharmacological modification. In further analysis, treatment with mucosolvan resulted in significantly decreasing postoperative pulmonary complications including lung infection, atelectasis due to mucus plugging of airway, respiratory failure, prolonged air leaks and pleural effusion. In contrast, the prevalence rate for an overall pulmonary complication was shown as 8% and 19% in the patients treated with and without mucosolvan, respectively. It was a 2.4-fold lower than the placebo-controlled patients, indicating that mucosolvan applied to perioperative respiratory management effectively prevented occurrence of respiratory problems from the patients with a reduced morbidity rate of the complication. Recent advances in understanding perioperative pathophysiology have indicated that multiple factors may be contributed to postoperative pulmonary complications with major improvements in surgical outcome[17,18]. Mucosolvan is a reliable and effective expectorant, which enables sticky phlegm to be removed from the respiratory system

faster and more easily by enhancing the bronchial secretions that loosen congested phlegm[19]. The agent also increases the body's production of surfactant, a substance that promotes the clearance mechanism for elimination of germs or other pathogens, which helps to prevent and overcome infection in the bronchi[11]. Several studies have indicated that postoperative pulmonary complications are the most frequently observed complications following lung resection[20-22], which is completely identical to our findings. Based on the fact that mucosolvan releases and strengthens the cilia, which can then expel the abnormal phlegm[23], it was reasonable to consider that mucosolvan minimized the risk of the pulmonary complications after major surgical procedures possibly through physiological clearance mechanisms of respiratory tract to provide the protection against lung infection and the infection-related diseases. Our results could provide important clues to mucosolvan'role in such airway perioperative management and thus may provide a novel therapy optimization to reduce pulmonary complications for the patients in the FTS program.

In terms of postoperative cardiac complications, an effect of mucosolvan on NSCLC patients in FTS was also examined because lung cancer surgery may cause damage to not only the lung but also other nearby organs including heart. The prevalence rate for the overall cardiac complication was shown as 9% and 12% in the patients treated with and without mucosolvan, respectively. There was no statistical difference seen in the rate between these two groups, suggesting that the effect of mucosolvan on the perioperative medical care mainly reduced pulmonary complications rather than cardiac complications in the patients undergoing the elective surgery. Our research indicated that cardiac complications did not occur much more often than pulmonary complications based on a low rate of the cardiac complications observed in the patients received FTS, which was consistent with the appearance of cardiac complications reported by another research[24].

The continuously growing pressure upon medical systems as a result of the increasing number of patients who need a surgical procedure and as a result of the economical restraint leads to FTS. Since the aim of FTS is to optimize the perioperative medical care for patients not only to reduce morbidity but also to enhance recovery of the patients after a surgical procedure[25], time for NSCLC patients staying in hospital was observed in the presence and absence of mucosolvan. Treatment with the agent resulted in significantly influencing time of hospital stay. There was an average value of a 4-day cut down for the stay may be observed as compared to the placebo-controlled patients, indicating that mucosolvan offered therapy optimization which greatly shortened the time required for full recovery. Since FTS is a multidisciplinary strategy which involves a combination of multiple factors including preoperative education, anesthetic, analgesic and pharmaceutical techniques, minimally invasive surgery and aggressive post-operative rehabilitation[26], it is conceivable that the combination therapy applied to the patients in FTS reduces hospitalization time and facilitates early recovery after the surgical procedures through the perioperative medical management including reducing the stress response, freezing intercostal nerves to control pain, and improving organ dysfunction and early removing drainage tube from the chest. Because mucosolvan only is an expectorant which is hardly linked to the reduced time of hospital stay, so the observation that mucosolvan reduced pulmonary complications was very important to clarification of shortening hospitalization time based on the findings that the patients after lung cancer resection had a high risk of postoperative pulmonary complications and prolonged air leaks, resulting in longer hospital stays[20,27]. Our results further revealed that mucosolvan may provide optimization therapy for airway perioperative management of the patients in FTS and benefit the process of entire treatment with reduced hospital costs especially for the patients with financial burden.

Conclusions

The use of mucosolvan is a feasible plan to optimize perioperative airway management for NSCLC patients in the FTS program through decreasing postoperative pulmonary complications and shortening hospitalization time with reduced hospital costs.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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