Original Article

Effects of beclomethasone and aminophylline combined with enteral nutrition in chronic obstructive pulmonary disease on nutritional status and immune function in elders

Can Peng BSc, Dongjie Xiao BSc, Haiyan Chen BSc, Lijie Rao BSc, Haiyan Xiao BSc, Huahua Li MSc

Department of Geriatrics, Hunan Provincial People's Hospital, First Affiliated Hospital of Hunan Normal University, Hunan, China

Background and Objectives: To investigate the efficacy of beclomethasone and aminophylline combined with enteral nutrition in the treatment of elderly patients with chronic obstructive pulmonary disease (COPD) and the associated effects of these drugs on patient nutritional status and immune function. **Methods and Study Design:** In total, 115 elderly patients with COPD were included and were randomized into an enteral nutrition (EN) group and a control (CON) group. Aminophylline, in combination with beclomethasone, was administered to the CON group, whereas aminophylline and beclomethasone in combination with EN was administered to the EN group. **Results:** Patients in the EN group showed significant improvement in partial pressure of carbon dioxide, forced expiratory volume in 1 sec/ expiratory forced vital capacity, and partial pressure of oxygen than those in the CON group. The levels of IgM, IgG, and IgA as well as the number of CD4+/CD8+ and CD4+/CD3+ T cells were higher in the EN group than those in the CON group ($p<0.05$); the EN group also exhibited higher levels of inflammatory cytokines, such as tumor necrosis factor-α and interleukin (IL)-1β ($p<0.05$), and lower levels of IL-6 than the CON group. In addition, patients in the EN group showed a significant increase in serum total protein, albumin, and transferrin levels than those in the CON group ($p<0.05$). **Conclusions:** Elderly patients with COPD showed a marked response to a regimen of beclomethasone, aminophylline, and EN, which significantly improved their immune function and nutritional status.

Key Words: aminophylline, beclomethasone, enteral nutrition, nutritional status, chronic obstructive pulmonary disease

INTRODUCTION

The incidence of chronic obstructive pulmonary disease (COPD) has accelerated in the last decade, posing a serious threat to the health of elderly individuals.[1] COPD is a chronic inflammatory lung disease commonly caused by smoking and is characterized primarily by progressive and persistent airflow obstruction.[2] Epidemiological surveys have shown that COPD will be the third leading cause of human mortality in the 2020s.[3] Currently, medications such as aminophylline, salbutamol, and beclomethasone are the principal treatments for COPD. The bronchodilatory effects of aminophylline and salbutamol significantly alleviate the condition.[4] Moreover, beclomethasone, as a current treatment option for asthma, can also be effective in treating recurrent episodes of wheezing, cough, chest tightness, and dyspnea through inhalation therapy.[5]

Patients with COPD often exhibit a long-term reaction to an inflammatory stimulus, have an altered cellular and humoral immunity, and show production of a large number of inflammatory factors, which promote neutrophil proliferation and activation.[6] Indeed, the levels of IgA, IgG, and IgM in vivo are highly correlated with the patient's immune function. Experiments have shown that patients with COPD have higher IgG and IgA levels than healthy controls and that humoral immunity plays a key role in the onset of COPD.[7]

Patients with COPD are also prone to malnutrition, which, combined with a weak immune system in elderly patients, often leads to infections or even severe respiratory and heart failure.[8] The prognostic outcomes of patients are closely related to the control of infection. Studies have demonstrated that 25–40% of patients with COPD were malnourished.[9] Studies focusing on patients with

Corresponding Author: Huahua Li, The Third Department of Geriatrics of Mawangdui Hospital District, Hunan Provincial People's Hospital, No.61 Jiefang West Road, Changsha City, Hunan Province, 410006, China.
Tel: +86-0731-84762748
Email: hteom5@163.com
Manuscript received 05 November 2020. Initial review completed 16 November 2020. Revision accepted 20 December 2020.
doi: 10.6133/apjcn.202103_30(1).0008

COPD found that nutritional support, in combination with conventional therapies, resulted in a significant increase in treatment efficacy.[10] However, little research has been performed regarding the use of enteral nutrition (EN) in the treatment course of patients with COPD.

In this study, we further analyzed the efficacy of beclomethasone and aminophylline combined with EN in the treatment of patients with COPD. Our measures included assessing the clinical therapeutic effects of the treatment, changes in patient immune function, and patient nutritional status.

METHODS

Study subjects

This study included elderly patients with COPD who were admitted to the Department of Respiratory Medicine in our hospital from March 2019 to March 2020. All patients met strict exclusion and inclusion criteria. Patients were informed of the risks of this study and signed consent forms were collected. After evaluation, the ethics committee of Hunan Provincial People's Hospital approved this study.

Inclusion and exclusion criteria

Inclusion criteria: GOLD diagnostic criteria for COPD: forced expiratory volume in 1 sec (FEV1) <50%, FEV1/expiratory forced vital capacity (FVC) <0.7; age >65 years. Exclusion criteria included patients with a history of diagnosed malignancy and asthma; unstable COPD; prostate cancer; benign prostatic hyperplasia; and history of cardiovascular, renal, hepatic, gastrointestinal, or endocrine disease, obesity, or surgery within 2 months prior to the study period (Figure 1).

Methods

This single-blind, single-center, randomized controlled trial categorized patients into a control group (CON group) and an EN group using the randomized number table method. The EN group was administered with aminophylline, beclomethasone, and EN. The group was also administered necessary general symptomatic measures, including, but was not limited to, relieving cough and asthma, treating infections, providing continuous low-flow oxygenation, and correcting acid-base and water-electrolyte imbalances.

The EN program was implemented as follows: the nutritionist created an individualized EN plan based on the patient's current biochemical test indicators and formulated a three-meal diet plan based on the patient's age, BMI index, and daily activity intensity. The nutritionist then observed the patient's condition changes and appropriately adjusted their diet and EN intake.

Common energy calculations for patients were as follows:

1) Energy supply was calculated according to the formula: daily calories required = expected value of H-B × activity coefficient (classified as bed rest 1.2; light activity 1.3; moderate activity coefficient 1.5; vigorous activity 1.75) × C (correction coefficient' 1.16 for males and 1.19 for females) × 1.2

2) The predicted value of H-B was calculated using the Harris Benedict formula:

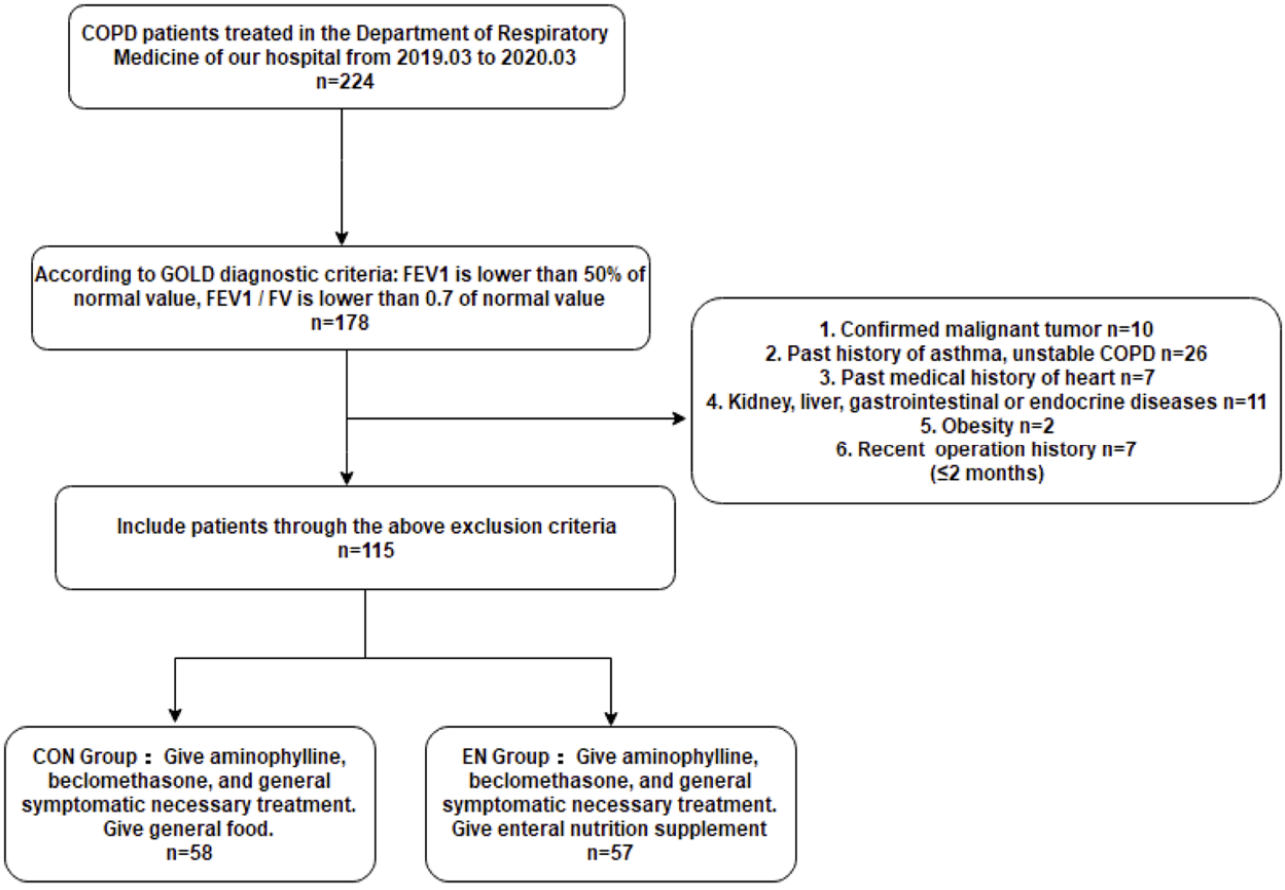

Figure 1. Flow chart of the study design as well as exclusion and inclusion criteria

Male daily energy requirement (kJ/d) = [66.47 + 5.0 × height (cm) + 13.75 × weight (kg) – 6.76 × age (years)] × 4.184

Female daily energy requirement (kJ/d) = {[55.1 + 1.85 × height (cm) + 9.56 × weight (kg) – 4.68 × age (years)] × 4.184

3) The Resul Enteral Nutrition Solution (Fresenius Kabi Deutschland GmbH, Germany, the main ingredients are shown in Table 1) was adopted as the basic preparation of EN for patients, and additional components (shown in Table 2) were added appropriately according to patient biochemical examination results.

4) Foods with a low respiratory quotient were chosen to avoid excessive carbon dioxide.

The CON group was administered aminophylline, beclomethasone, and routine treatments as described in the EN group. The patients in this group received normal food.

Randomization and blinding

A random table was generated using SPSS 23.0 (SPSS Inc., Chicago, Illinois, USA) and was used to sequentially enroll eligible participants in order of patient admission. It was also used to categorize patients into the CON and EN groups in a 1:1 ratio. The researchers grouped the patients and informed the physicians.

Observation indicators

Pulmonary function-related tests

The partial pressure of carbon dioxide (PaCO2), FEV1/FVC, and partial pressure of oxygen (PaO2) were determined in the hospital's pulmonary examination room before and after 4 weeks of treatment.

Immune function assay

Fasting blood was collected each morning for 4 consecutive weeks. The samples were allowed to sit for approximately 30 min in a cool, dark environment before centrifuging at 3,000 rpm for 10 min to obtain the serum, which was immediately stored at -80°C. The levels of serum IgM, IgG, and IgA were determined using the TIIA method. The FCM method was used to detect the levels of different T cell subgroups, and all operations were performed in strict accordance with the instructions.

We further investigated the levels of inflammatory factors, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β in the serum of the participants according to the corresponding kit instructions (Jiangsu Edisha Biochemical Reagents Company).

Monitoring indicators related to nutritional status

Fasting blood samples collected from study participants for 4 consecutive weeks were sent to the hospital laboratory for determining total protein, albumin, and transferrin.

Statistical analysis

Data analysis was performed using SPSS 23.0 (SPSS Inc.). Student's t-test was employed to analyze differences between groups, while the rank-sum test was used to validate and analyze ranked data between groups. Counted data were analyzed using the χ^2 test. Measurements were expressed as means ± standard deviations (mean ± SD). Results with $p<0.05$ were considered statistically significant.

RESULTS

Comparison of baseline data

One hundred and fifteen patients with COPD treated at our hospital were enrolled in this study and randomly assigned to the CON group (N=58) or the EN group (N=57). All patients completed the study. Baseline data, including age, sex, smoking and alcohol history, and medical history, were not statistically different between the two groups ($p>0.05$) (Table 3).

Inter-group comparison of lung function indicators

Before treatment, differences in lung function indicators between the two groups were not significant. After treatment, PaCO2, FEV1/FVC, and PaO_2 were significantly improved in the EN group than in the CON group ($p<0.05$), suggesting that EN could help improve pul-

Table 1. Components of the enteral nutrition solution

Constituent	Content/100 mL solution
Protein	3.8 g
Fat	3.4 g
Saturated fatty acids	1.6 g
Unsaturated fatty acids	1.3 g
Medium chain triglycerides	1.2 g
Carbohydrates	13.8 g
Sugar	0.5 g

Table 2. Various components used

Component name	Application
Concentrated whey protein powder	Whey protein concentrate
Trace elements	Human body requires various mineral trace elements
Vitamins	Contains various fat-soluble vitamins as well as vitamin B and C
Dietary fibers	Contains dietary fiber combination
Probiotic components	Contains seven probiotic combinations
MCT	Contains 8-carbon and 10-carbon fatty acids
NHA	NHA's omega-3 unsaturated fatty acids

Table 3. General baseline patient information

Parameter	CON group	EN group	*p* value
Male/Female	26/32	27/31	0.632
Age (years)	68.3±4.3	68.2±4.6	0.638
BMI (kg/cm^2)	20.6±1.3	20.5±1.4	0.676
Age (years)	59.2±6.1	60.1±5.8	0.176
Smoking (yes/no)	21/48	22/47	0.698
Drinking (yes/no)	27/42	26/42	0.679
Insomnia time (months)	4.32±0.13	4.28±0.28	0.283

Data are expressed as n or mean±SD.

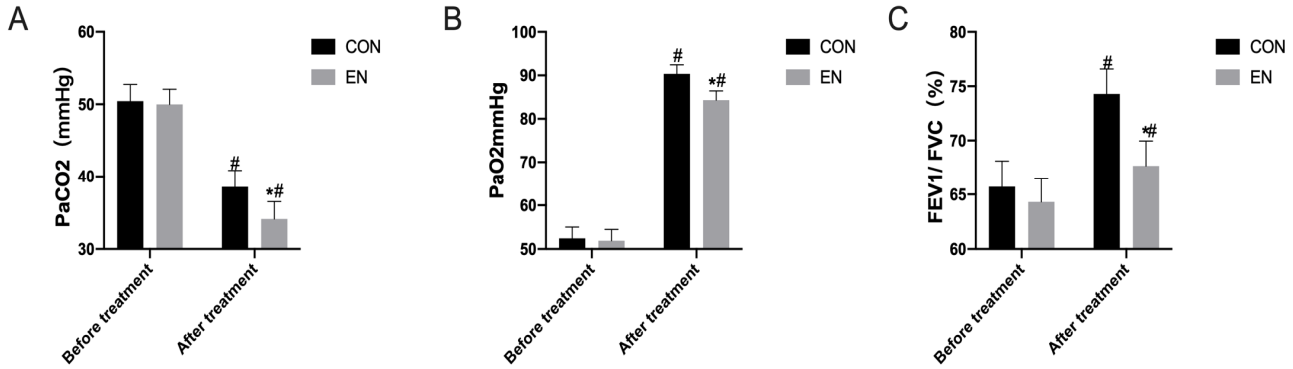

Figure 2. Comparison of the pulmonary function-related indexes between the enteral nutrition (EN) and control (CON) groups. A. $PaCO_2$. B. PaO_2. C. FEV1/FVC. $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; FEV1/FVC: forced expiratory volume in 1 sec/forced vital capacity; CON: control group; EN: enteral nutrition group; $^*p<0.05$ compared with the CON group. $^\#p<0.05$ compared with the pre-treatment group.

monary function in elderly patients with COPD (Figure 2).

Inter-group comparisons of immune function

Immune function was not significantly different between the groups before treatment. After completion of treatment, the EN group showed higher IgM, IgG, and IgA levels as well as increased CD4+/CD8+ and CD4+/CD3+ T cell counts than the CON group, suggesting that patients with COPD showed a significant recovery of immune function after EN support. Moreover, the levels of inflammatory cytokines such as IL-1β and TNF-α increased ($p<0.05$), whereas those of IL-6 decreased in the EN group than in the CON group ($p<0.05$) (Figure 3-5).

Inter-group comparisons of nutritional status

Total protein and serum albumin did not differ significantly between the two groups before treatment. After 4 weeks, the EN group exhibited a significant increase in total protein and serum albumin than the CON group (Figure 6). Our findings are shown in the conceptual diagram (Figure 7).

DISCUSSION

The elderly are especially prone to the adverse health effects of COPD. Studies have found that the nutritional status of patients improves rapidly after receiving EN and their lung function also improves significantly.[11] When comparing the efficacy of a commonly used treatment

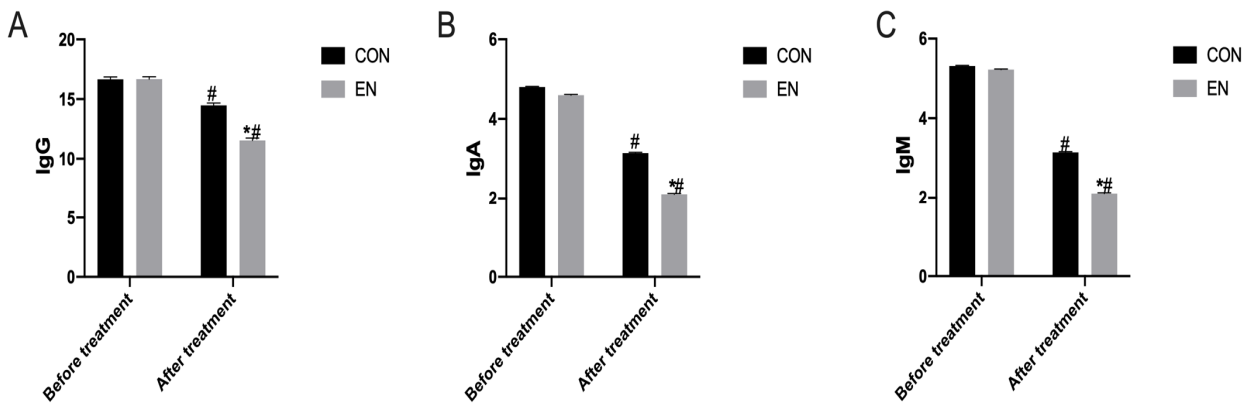

Figure 3. Comparison of the humoral immune function-related indexes between the enteral nutrition (EN) and control (CON) groups. A. Changes in IgG levels before and after enteral nutrition treatment. B. Changes in IgA levels before and after enteral nutrition treatment. C. Changes in IgM levels before and after enteral nutrition treatment. CON: control; EN: enteral nutrition group. $^*p<0.05$ compared with the CON group. $^\#p<0.05$ compared with the pre-treatment group.

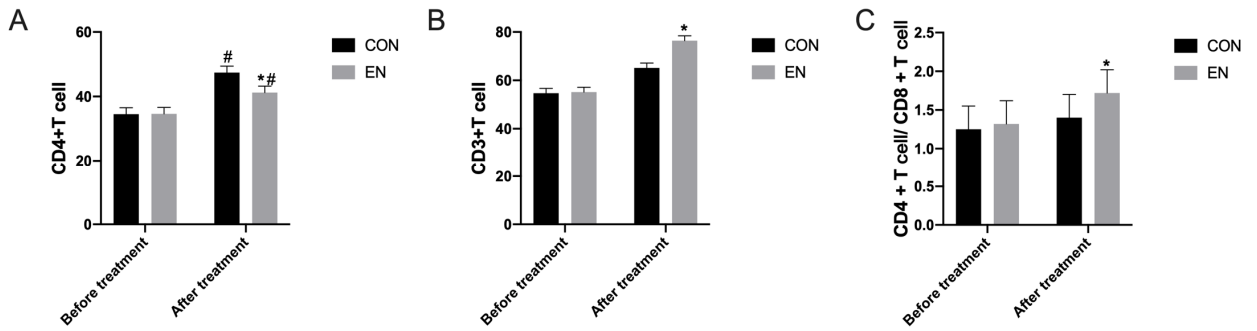

Figure 4. Comparison of the cellular immune function-related indexes between the enteral nutrition (EN) and control (CON) groups. A. Changes in the levels of CD3+ T cells before and after enteral nutrition treatment. B. Changes in the levels of CD4+ T cells before and after enteral nutrition treatment. C. Changes in the levels of CD4+/CD8+ T cells before and after enteral nutrition treatment. CON: control group; EN: enteral nutrition group. $^{*}p<0.05$ compared with the CON group. $^{\#}p<0.05$ compared with the pre-treatment group.

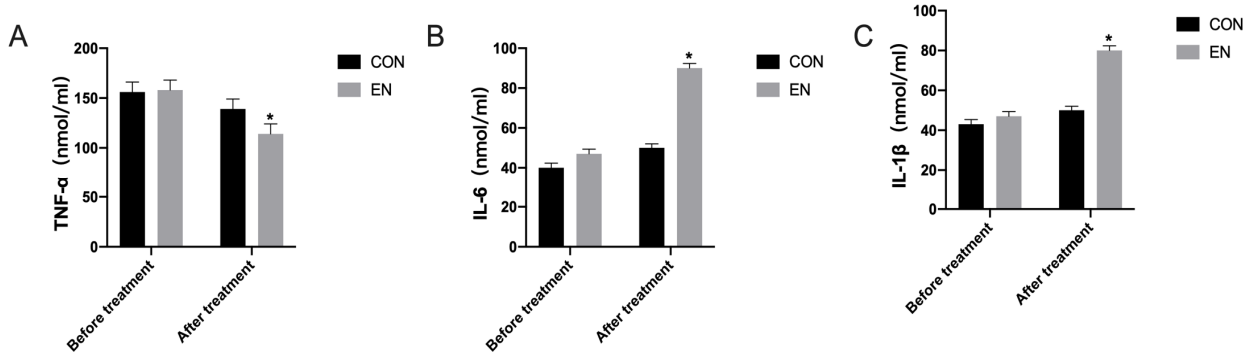

Figure 5. Comparison of serum inflammatory cytokine indexes in the enteral nutrition (EN) and control (CON) groups. A. Changes in serum inflammatory cytokine TNF-α levels before and after enteral nutrition treatment. B. Changes in serum inflammatory cytokine IL-1β levels before and after enteral nutrition treatment. C. Changes in serum inflammatory cytokine IL-6 levels before and after enteral nutrition treatment. CON: control group; EN: enteral nutrition group; TNF-α: tumor necrosis factor-α; IL-6: interleukin-6; IL-1β: interleukin-1β. $^{*}p<0.05$ compared with the CON group. $^{\#}p<0.05$ compared with the pre-treatment group.

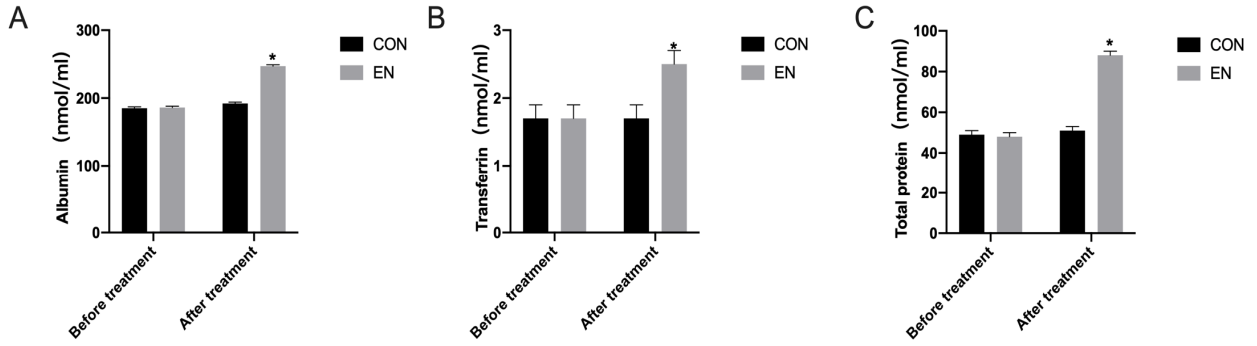

Figure 6. Comparison of the nutritional status of the enteral nutrition (EN) and control (CON) groups. A. Changes in albumin levels before and after enteral nutrition treatment. B. Changes in transferrin levels before and after enteral nutrition treatment. C. Changes in total protein before and after enteral nutrition treatment. CON: control group; EN: enteral nutrition group. $^{*}p<0.05$ compared with the CON group; $^{\#}p<0.05$ compared with the pre-treatment group.

regimen (beclomethasone + aminophylline) with beclomethasone + aminophylline + EN, we found that the $PaCO_2$, FEV1/FVC, and PaO_2 were improved significantly in the EN group than those in the CON group. The levels of IgM, IgG, and IgA, which are related to humoral immunity, were higher in the EN group than those in the CON group. Moreover, there was an increased number of CD4+/CD8+, CD4+, and CD3+ T cells in the EN group, indicating that EN accelerated the recovery of cellular immune function. The levels of TNF-α and IL-1β were higher in the EN group than in the CON group ($p<0.05$), whereas IL-6 levels were significantly lower in the EN group than in the CON group ($p<0.05$). Moreover, the EN group had significantly higher serum total protein, albumin, and transferrin levels than the CON group.

When elderly patients with COPD develop severe malnutrition, they are also at a very high risk of developing infections.[12] Studies related to pulmonary function have found that the resistance in patient airways increases significantly during acute exacerbations, severely decreasing compliance, which further increases airway resistance owing to excessive secretions and reduction in pulmonary function.[13] It has also been noted that elderly patients with COPD are often severely malnourished, have significant

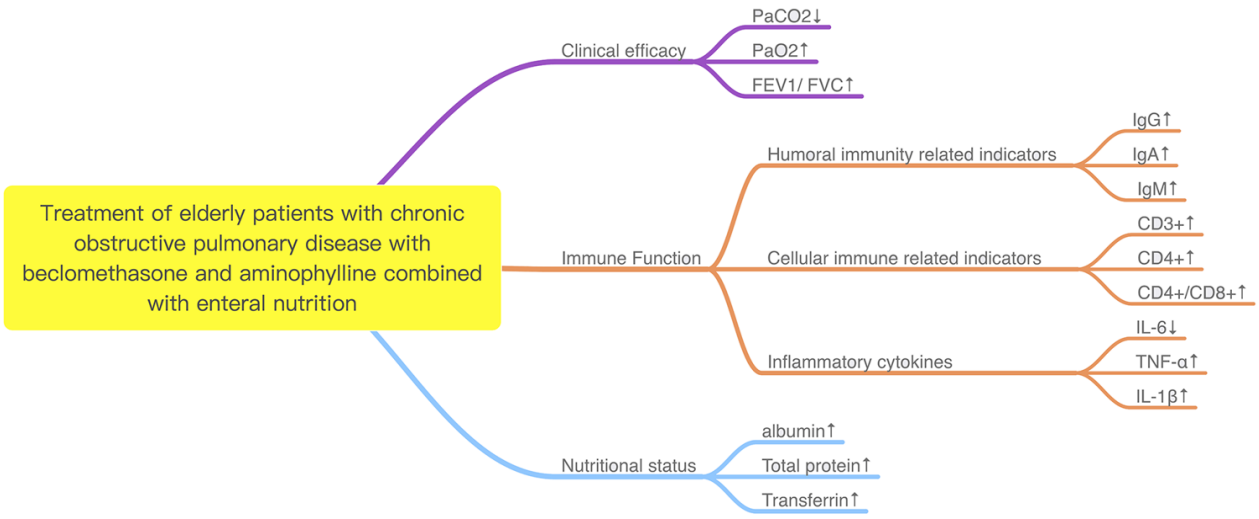

Figure 7. Conceptual diagram to summarize the findings. ↑: EN group is higher than CON group; ↓: EN group is lower than CON group; CON: control group; EN: enteral nutrition group.

atrophy of the respiratory muscles such as the intercostal muscles and diaphragm, and show a severe decrease in pulmonary ventilation.[14] In addition, lung compliance is greatly reduced because of the decrease in the amount of pulmonary surfactant and the number of elastic fibers in the lung tissue. Patients also have difficulty breathing owing to poor lung diffusion. Lung function further deteriorates as COPD progresses, and the prognosis only gets worse.[15] However, previous clinical studies have shown that EN therapy is effective in improving lung function in patients with COPD.[16]

The lung function scores between the EN and CON groups were not significantly different prior to treatment; however, all were substantially lower than the normal value. Patients who received EN exhibited significantly improved lung function, which was consistent with the results of a previous study. The beneficial effects of good nutrition on lung function may be derived from improved nitrogen balance, increased amount of muscle protein, increased energy to the respiratory muscles, and reduced fatigue, ultimately restoring lung function. Moreover, previous studies have found that increasing the fat emulsion dosage increases caloric intake; decreases protein breakdown, carbon dioxide production, and respiratory quotient; and improves lung function.[17,18]

A follow-up study on COPD found that chronic inflammatory responses are present and persist for a very long time in most patients with COPD.[19] They also found that the development of an inflammatory response in patients with COPD is closely related to malnutrition. Indeed, the immunity of patients with COPD is significantly improved after nutritional therapy. Additionally, improved nutrition reduced patient inflammation, accelerated recovery of an intact epithelium, decreased inflammatory cytokines, and improved patient prognosis compared with conventional treatments.[20] The results of our study showed that the immunity of patients with COPD in the EN group was significantly improved than that of patients in the CON group. When patients were malnourished, lymphocyte and antibody production was severely suppressed and their humoral and cellular immune functions were significantly inhibited. Patients were supplemented with omega-3 fatty acids in this study, which caused the suppression of proteolysis and the secretion of tumor-associated factors that promote cachexia, enhancing immune function.[21] Upon receiving proper nutrition, patients displayed increased levels of IgA, T lymphocytes, and cytokines, which resulted in a significant improvement in their immune function.

Some scholars have found that the levels of transferrin and albumin increased significantly after receiving EN.[22] The results of this study show that patients treated with EN therapy had higher levels of transferrin and albumin than those treated with EN solution alone. Patients using aminophylline as well as beclomethasone showed a substantial increase in total body protein, serum protein, albumin, and transferrin, which is consistent with the results of the above-mentioned study. Previous studies have also shown that as a carrier of iron ions, transferrin not only promotes erythropoiesis and blood cell maturation but also enhances hematopoiesis.[23] Albumin is responsible for maintaining colloidal osmotic pressure and is involved in regulating the synthesis of many substances.[24] Thus, patients treated with EN exhibited improved nutritional status, enhanced anabolic processes, and improved hematopoiesis, thus having a better prognosis.

This study does have several limitations. First, we have not fully elucidated the mechanism by which the combination of beclomethasone and aminophylline with EN was successful in the treatment of COPD in the elderly. In addition, this study is a single-center randomized clinical controlled trial, and multiple large-scale randomized, controlled studies are needed to further validate our results.

In conclusion, our results show that beclomethasone and aminophylline combined with EN can effectively improve pulmonary dysfunction, immunity, nutritional status, and the condition of elderly patients with COPD.

AUTHOR DISCLOSURES

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This work was supported by Changsha City Science and Technology Foundation (Grant/Award Number: kq1907069)

and Hunan Province Health Committee Research Projects (Grant/Award Number: 20200220).

REFERENCES

1. Poh TY, Mac Aogáin M, Chan AK, Yii AC, Yong VF, Tiew PY, Koh MS, Chotirmall SH. Understanding COPD-overlap syndromes. Expert Rev Respir Med. 2017;11:285-98. doi: 10.1080/17476348.2017.1305895.
2. Soriano JB, Polverino F, Cosio BG. What is early COPD and why is it important? Eur Respir J. 2018;52:1801448. doi: 10.1183/13993003.01448-2018.
3. Mammen MJ, Sethi S. COPD and the microbiome. Respirology. 2016;21:590-9. doi: 10.1111/resp.12732.
4. Neame M, Aragon O, Fernandes RM, Sinha I. Salbutamol or aminophylline for acute severe asthma: how to choose which one, when and why? Arch Dis Child Educ Pract Ed. 2015;100:215-22. doi: 10.1136/archdischild-2014-306186.
5. Beeler C. Drugs and lactation database: LactMed. Journal of Electronic Resources in Medical Libraries. 2012;9:272-7. doi: 10.1080/15424065.2012.735134.
6. Bozinovski S, Vlahos R, Anthony D, McQualter J, Anderson G, Irving L, Steinfort D. COPD and squamous cell lung cancer: aberrant inflammation and immunity is the common link. Br J Pharmacol. 2016;173:635-48. doi: 10.1111/bph.13198.
7. Cheng G, Zhang N, Wang Y, Rui J, Yin X, Cui T. Antibodies of IgG, IgA and IgM against human bronchial epithelial cell in patients with chronic obstructive pulmonary disease. Clin Lab. 2016;62:1101-8. doi: 10.7754/clin.lab.2015.151020.
8. Mete B, Pehlivan E, Gülbaş G, Günen H. Prevalence of malnutrition in COPD and its relationship with the parameters related to disease severity. Int J Chron Obstruct Pulmon Dis. 2018;13:3307-12. doi: 10.2147/copd.S179609.
9. Perrot L, Greil A, Boirie Y, Farigon N, Mulliez A, Costes F, Caillaud D. Prevalence of sarcopenia and malnutrition during acute exacerbation of COPD and after 6 months recovery. Eur J Clin Nutr. 2020;74:1556-64. doi: 10.1038/s41430-020-0623-6.
10. Ingadottir AR, Beck AM, Baldwin C, Weekes CE, Geirsdottir OG, Ramel A, Gislason T, Gunnarsdottir I. Oral nutrition supplements and between-meal snacks for nutrition therapy in patients with COPD identified as at nutritional risk: a randomised feasibility trial. BMJ Open Respir Res. 2019;6:e000349. doi: 10.1136/bmjresp-2018-000349.
11. Nguyen HT, Collins PF, Pavey TG, Nguyen NV, Pham TD, Gallegos DL. Nutritional status, dietary intake, and health-related quality of life in outpatients with COPD. Int J Chron Obstruct Pulmon Dis. 2019;14:215-26. doi: 10.2147/copd.S181322.
12. Sehgal IS, Dhooria S, Agarwal R. Chronic obstructive pulmonary disease and malnutrition in developing countries. Curr Opin Pulm Med. 2017;23:139-48. doi: 10.1097/mcp.0000000000000356.
13. Jerng JS, Tang CH, Cheng RW, Wang MY, Hung KY. Healthcare utilization, medical costs and mortality associated with malnutrition in patients with chronic obstructive pulmonary disease: a matched cohort study. Curr Med Res Opin. 2019;35:1265-73. doi: 10.1080/03007995.2019.1574460.
14. Hoong JM, Ferguson M, Hukins C, Collins PF. Economic and operational burden associated with malnutrition in chronic obstructive pulmonary disease. Clin Nutr. 2017;36:1105-9. doi: 10.1016/j.clnu.2016.07.008.
15. Luo Y, Zhou L, Li Y, Guo S, Li X, Zheng J et al. Fat-free mass index for evaluating the nutritional status and disease severity in COPD. Respir Care. 2016;61:680-8. doi: 10.4187/respcare.04358.
16. Ter Beek L, van der Vaart H, Wempe JB, Dzialendzik AO, Roodenburg JL, van der Schans CP, Keller HH, Jager-Wittenaar H. Dietary resilience in patients with severe COPD at the start of a pulmonary rehabilitation program. Int J Chron Obstruct Pulmon Dis. 2018;13:1317-24. doi: 10.2147/copd.S151720.
17. Hsieh MJ, Yang TM, Tsai YH. Nutritional supplementation in patients with chronic obstructive pulmonary disease. J Formos Med Assoc. 2016;115:595-601. doi: 10.1016/j.jfma.2015.10.008.
18. Shepherd AB, Bowell K. 'Mind the gap': the importance of managing malnutrition in chronic obstructive pulmonary disease. Br J Nurs. 2019;28:1442-9. doi: 10.12968/bjon.2019.28.22.1442.
19. Zong L, Li H, Li S. Effects of neoadjuvant chemotherapy combined with enteral nutrition on perioperative immunity, inflammation and intestinal flora in gastric cancer patients. J BUON. 2019;24:1113-9. PMID: 31424669.
20. Zhou H, Qian H. Relationship between enteral nutrition and serum levels of inflammatory factors and cardiac function in elderly patients with heart failure. Clin Interv Aging. 2018;13:397-401. doi: 10.2147/CIA.S157507.
21. Cheng Y, Zhang J, Zhang L, Wu J, Zhan Z. Enteral immunonutrition versus enteral nutrition for gastric cancer patients undergoing a total gastrectomy: A systematic review and meta-analysis. BMC Gastroenterol. 2018;18:11. doi: 10.1186/s12876-018-0741-y.
22. Yang F, Wei L, Huo X, Ding Y, Zhou X, Liu D. Effects of early postoperative enteral nutrition versus usual care on serum albumin, prealbumin, transferrin, time to first flatus and postoperative hospital stay for patients with colorectal cancer: A systematic review and meta-analysis. Contemp Nurse. 2018;54:561-77. doi: 10.1080/10376178.2018.1513809.
23. Kawabata H. Transferrin and transferrin receptors update. Free Radic Biol Med. 2019;133:46-54. doi: 10.1016/j.freeradbiomed.2018.06.037.
24. Erstad BL. Albumin disposition in critically Ill patients. J Clin Pharm Ther. 2018;43:746-51. doi: 10.1111/jcpt.12742.