Original Article

Anti-inflammatory and anticatabolic effects of short-term β-hydroxy-β-methylbutyrate supplementation on chronic obstructive pulmonary disease patients in intensive care unit

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Elevated inflammatory markers and muscle wasting were common in chronic obstructive pulmonary disease (COPD) patients. The purpose of this study was to investigate the effect of 7-day β-hydroxy-β-methylbutyrate (HMB) supplementation on inflammation, protein metabolism, and pulmonary function in COPD patients in an intensive care unit. Thirty-four COPD patients who required mechanical ventilators were randomly assigned to HMB (n=18) or control (n=16) groups. The HMB group received HMB 3 g/d for 7 days. White blood cell count, C-reactive protein, and creatinine were significantly lower, while cholesterol and total protein were significantly higher after HMB supplementation. The body weight remained unchanged in both groups. Ten subjects (55.6%) in the HMB group and 4 subjects (25.0%) in the control group had improved pulmonary function, indicated by their ventilator modes. This short-term study suggests that HMB supplementation may have anti-inflammatory and anticatabolic effect and improve pulmonary function in COPD patients in an intensive care unit setting.

Key Words: β-hydroxy-β-methylbutyrate, inflammation, C-reactive protein, chronic obstructive pulmonary disease

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity worldwide and affects more than 14 million patients in the United States alone.[1] It is estimated to become the fifth leading cause of death and disability worldwide by the year 2020.[2] Several inflammatory markers, including C-reactive protein (CRP),[3] leukocyte count,[3] tumor necrosis factor (TNF)-α[4-6], soluble TNF-α receptors,[3,6] and lipopolysaccharide binding protein,[3,7] have been shown to be elevated in patients with COPD. The increased TNF-α production was thought be linked to tissue hypoxia.[6] Muscle wasting is also common in COPD patients[8] and has been linked to increased mortality, independent of lung function.[9] In addition to increased basal metabolism, resulting from higher energy cost of breathing,[10,11] systemic inflammation, tissue hypoxia, physical inability,[12] elevated whole-body protein turnover,[13] and imbalance in plasma and muscle amino acid concentrations[7] were all thought to play a role in muscle wasting in these patients.

Nutritional support, with the aim to prevent muscle wasting and/or increase lean body mass, have had limited success in COPD patients. The weight gains after 1 to 4 months of aggressive nutritional support were usually less than 5 kg.[12] The high dietary calorie intake was intolerable in many COPD patients due to the increased CO_2 production and breath load.[14] A high incidence of gastrointestinal complications, such as bloating, early satiety and postprandial dyspnea, further limited the consumption of calories and nutrients.[15] Therefore, other therapeutic agents or methods may be considered in combination with regular nutritional support to prevent muscle wasting in COPD patients.

β-hydroxy-β-methylbutyrate (HMB) is a derivative of leucine, metabolized from its transamination product, β-ketoisocaproate.[16] Several animal and human studies have implicated anticatabolic effect of HMB on skeletal muscles.[16-18] Most human studies have showed that supplementation of HMB for 2-7 weeks during weight training programs can increase muscle mass and/or decrease muscle

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Table 1. Pulmonary functions and arterial blood gases of HMB and control groups at baseline and after the 7-day study period (mean ± standard deviation)

	HMB (N = 18)		Control (N = 16)	
	Baseline	After	Baseline	After
P_I (cm H_2O)	-19.44 ± 10.86	-19.83 ± 13.01	-15.69 ± 7.98	-13.63 ± 7.97
P_E (cm H_2O)	20.11 ± 8.36	21.50 ± 11.69	19.63 ± 9.21	21.94 ± 6.24
FiO_2 (%)	54.44 ± 23.07	40.00 ± 16.33	51.25 ± 23.98	46.45 ± 24.51
PaO_2 (mm Hg)	101.69 ± 40.43	91.21 ± 16.88	126.85 ± 49.08	107.35 ± 28.07
$PaCO_2$ (mm Hg)	43.13 ± 15.89	40.68 ± 5.60	35.89 ± 11.93	41.16 ± 15.22*
SaO_2 (%)	96.75 ± 3.18	97.17 ± 1.45	97.77 ± 1.67	97.39 ± 1.45

P_I, static inspiratory pressure; P_E, static expiratory pressure; FiO_2, inspired oxygen concentration; PaO_2, arterial oxygen pressure; $PaCO_2$, arterial carbon dioxide pressure; SaO_2, oxygen saturation. *After vs baseline within the same group; P<0.01.

breakdown.[17,19-21] A clinical study suggested that in human immunodeficiency virus (HIV)-infected patients, a combination of 3g HMB, 14g glutamine, and 14g arginine resulted in significant increases in body weight, fat free mass, and immune status, compared to the placebo group after 8 weeks.[22] It has been speculated that the anticatabolic effect of HMB was to reduce skeletal muscle proteolysis, although no specific mechanism has been demonstrated.[18] In addition, HMB has been suggested to enhance lymphocyte blastogenesis in vitro[16,23] and nitrite production in macrophage and antibody production in chickens.[24]

The potential anticatabolic effect of HMB may reduce muscle wasting and help the weaning from ventilators in COPD patients. The purpose of this study was to investigate the effect of 3 g/d HMB supplementation for 7 days on inflammation, protein metabolism, and pulmonary function in COPD patients in an intensive care unit (ICU) setting. The dose of 3 g/d was selected for this study because it has been shown to be effective in most literatures[17,19-21] and well-tolerated even in very weak patients.[22]

Materials and methods

Subjects

COPD patients were recruited from the ICU of Kaohsiung Municipal United Hospital, Kaohsiung, Taiwan. All subjects were clinically diagnosed with COPD and free of cancer, liver disease, chronic renal failure and sepsis. All subjects had a history of COPD for at least 5 years. They were admitted to ICU due to complications requiring mechanical ventilators. The first 36 COPD patients admitted to ICU, after the beginning of the study period, were recruited. The randomization was achieved by assigning the subjects to HMB or control groups in alternative order of their admission to ICU. That is, the odd-numbered admissions were assigned to HMB group, whilst the even-numbered were assigned to control group. Thirty-four subjects, including 18 in HMB (11 males, 7 females) and 16 in control (10 males, 6 females) groups, completed the study. Two female subjects in the control group transferred to other hospitals for personal reasons during the study period. The HMB group received HMB (calcium salt, Musashi, Vicoria, Australia) 3g/d for 7 days, in 2 equal daily doses given through a nasogastric feeding tube after lunch and dinner by nurses under the supervision of dietitians. This study was approved by the review board of Kaohsiung Municipal United Hospital. All subjects signed an informed consent after the nature of the procedures had been explained. The procedures followed were in accordance with the Declaration of Helsinki in 1995, as revised in Edinburgh 2000. All subjects gave informed consent after the procedure and risks of the study were clearly explained.

The settings of ventilators, including inspired oxygen concentration (FiO_2), mode of ventilation, pressure, volume, and respiration rate were determined by physicians and respiratory technicians according to each patient's physiological conditions. The physicians and respiratory technicians were completely blind to which group the subjects were in. All subjects were fed mixed commercial formulas, containing 30% calorie from carbohydrate, 47% from fat, and 23% from protein (1330 kcal/L). The daily intake was recorded by nurses. Body weight was measured with bed scales. Biochemical parameters, pulmonary function, and body weight were measured before and after the 7-day study period.

Blood analysis

Biochemical parameters of fasting venous blood were measured in the clinical laboratory of the hospital with standard protocols using an automatic analyzer (Hitachi, Japan). CRP was measured with an immunoturbidimetric method using a commercial kit (DiaSys diagnostic, Holzheim, Germany).

Pulmonary functions

The blood sampling and measurement of minute ventilation and static inspiratory and expiratory pressure (P_I and P_E, respectively) were performed by a trained nurse. Arterial blood was withdrawn in the morning after an overnight fast when the patients were breathing air from ventilators. The arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), and pH were measured with a blood gas analyzer (AVL, Graz, Austria). Minute ventilation was measured with a respirometer (Ferraris

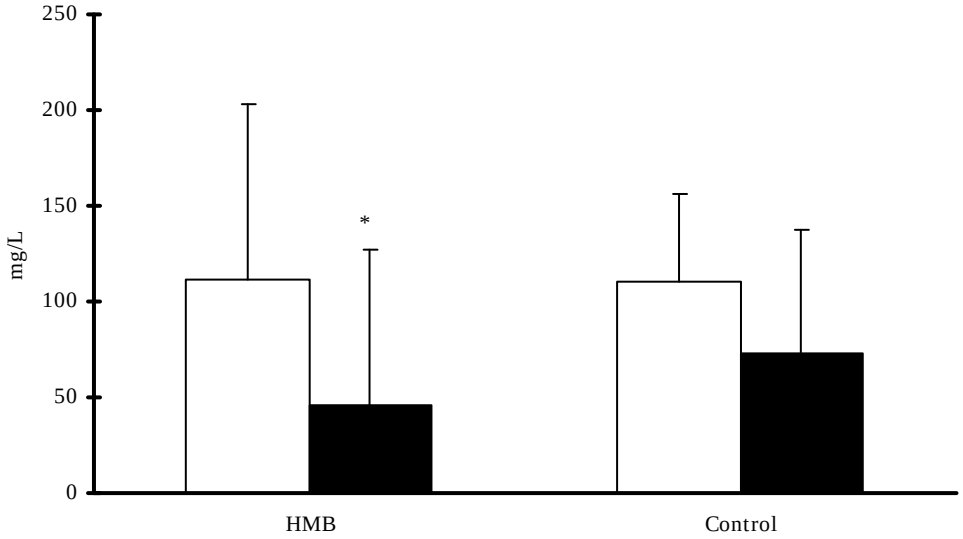

Figure 1. Plasma CRP concentration at baseline and after the 7-day study period in HMB and control groups. Open bar: baseline, close bar: after supplementation. *p<0.05, after vs baseline within the same group.

Medical Inc., Louisville, CO, USA). P_I and P_E were measured with an inspiratory force meter (Boehringer Laboratories Inc., Norristown, PA, USA).

Statistical analysis

The variables before and after the treatment within each group were analyzed by paired t-test. The percentages of subjects with improved and maintained or deteriorated pulmonary functions in the 2 groups were compared with Fisher's exact test. Baseline levels of all variables between the 2 groups were analyzed by t-test. The magnitude of change of variables was calculated as (after – baseline)/baseline. The magnitude of change of the 2 groups was analyzed by regression analysis, controlling for baseline BMI. All analysis was performed using SPSS 11.0 for Windows (Chicago, IL, USA). A *P* value <0.05 was considered significant. All measured variables are expressed as mean ± SD.

Results

The age of subjects in HMB and control groups was 78.8 ± 9.7 and 78.3 ± 7.4 years, respectively (data not shown). The height of subjects was 1.58 ± 0.09 m in HMB group and 1.62 ± 0.09 m in control group (data not shown). There was no significant difference in age or height between the groups. Table 1 shows the pulmonary function and arterial blood gas measurements of HMB and control groups at the baseline and after the study period. $PaCO_2$ was significantly higher after 7 days in the control group. There was no significantly difference at baseline between the HMB and control groups in all pulmonary parameters.

Blood parameters and body weight of HMB and control groups before and after the study period are presented in Table 2. The HMB group had significantly higher body weight (*P* = 0.048) and marginally significantly higher BMI (*P* = 0.056) at baseline than the control group. To avoid the potential effect of the difference in nutritional status on biochemical parameters, regression analysis was used to control for baseline BMI. White blood cell count and creatinine were significantly lower and cholesterol significantly higher after HMB, supplementation compared to baseline. The magnitude of change between the 2 groups were marginally significantly different in white blood cell count (*P* = 0.074) and cholesterol (*P* = 0.063), after controlling for baseline BMI. The body weight remained unchanged after the study in both groups. There was no significant difference in average daily caloric intake during the study period (2066.5 ± 362.4 and 2175.3 ± 399.6 kcal for HMB and control group, respectively). CRP was significantly lower after HMB supplementation, but remained unchanged in the control group (baseline vs after: 111.56 ± 91.47 vs 46.19 ± 45.29 mg/L in HMB group; 110.59 ± 81.35 vs 72.65 ± 64.72 mg/L in control group) (Fig. 1). The magnitude of change in CRP between the 2 groups was similar after controlling for baseline BMI.

Ten subjects in the HMB group and 4 subjects in control group had improved pulmonary functions since their ventilators were changed from pressure control ventilation (PCV) or assist/control (A/C) mode to pressure support ventilation (PSV) or synchronized intermittent mandatory ventilation (SIMV)+PSV mode (Table 3). Seven subjects (38.9%) in HMB group and 12 subjects (75%) in the control group remained at the same ventilator mode after the study. One subject (5.6%) in the HMB group showed deteriorated pulmonary function as his ventilator was changed from SIMV+PSV mode to A/C mode. When the subjects with maintained and deteriorated pulmonary functions were pooled together, the percentage of subjects with improved pulmonary function in HMB group was marginally significantly higher than that in the control group (*P* =0.092).

Discussion

In this group of elderly COPD patients, supplementation of HMB at 3 g/d for 7 days may reduce inflammation and improve pulmonary function. CRP and white blood cell count were significantly reduced in the HMB group after the study period. The acute-phase protein CRP, a sensitive marker for early inflammation,[25] has been shown to be elevated in COPD patients,[3] especially during exacerbation.[26] Several other markers of inflammation were

Table 2. Blood parameters and body weight of HMB and control groups at baseline and after the 7-day study period (mean±standard deviation)

	HMB (N = 18)		Control (N = 16)	
	Baseline	After	Baseline	After
White blood cell ($10^3/mm^3$)	14.00 ± 6.63	9.64 ± 3.19**	12.21 ± 4.04	11.10 ± 5.17‡
Hemoglobin (g/L)	104.32 ± 20.67	102.44 ± 15.53	104.07 ± 26.82	96.12 ± 11.50
Hematocrit (%)	32.35 ± 6.72	31.26 ± 4.72	31.46 ± 7.68	29.90 ± 4.50
Cholesterol (mmol/L)	3.28 ± 1.10	3.61 ± 1.02*	2.98 ± 0.99	3.03 ± 0.96‡
Triacylglycerol (mmol/L)	0.84 ± 0.38	0.84 ± 0.44	0.84 ± 0.31	0.82 ± 0.33
Blood urea nitrogen (mg/L)	282.78 ± 158.14	237.2 ± 119.8	295.69 ± 195.76	280.63 ± 256.06
Creatinine (mg/L)	10.33 ± 9.60	8.17 ± 7.10*	8.94 ± 6.18	9.19 ± 9.05
GOT (U/L)	43.17 ± 50.99	29.76 ± 17.09	31.13 ± 17.96	35.56 ± 19.17
GPT (U/L)	38.28 ± 46.06	36.47 ± 35.41	28.25 ± 22.96	36.25 ± 25.92
Total bilirubin (mg/L)	11.46 ± 16.29	6.21 ± 3.81	7.80 ± 5.33	6.79 ± 4.44
Direct bilirubin (mg/L)	4.58 ± 5.14	3.74 ± 3.17	4.93 ± 3.47	4.71 ± 3.39
Uric acid (mg/L)	43.00 ± 32.68	39.88 ± 24.66	55.56 ± 41.22	46.75 ± 37.55
Body weight (kg)	53.08 ± 8.43†	53.72 ± 9.26	46.88 ± 9.14	46.77 ± 7.82
Body mass index (kg/m^2)	21.10 ± 3.72	21.20 ± 3.81	18.69 ± 3.33	18.53 ± 2.96

*P<0.05; ** P <0.01, after vs baseline within the same group. †Significantly different from control group at baseline. ‡ P <0.1, magnitude of change between HMB and control groups after controlling for baseline BMI.

also elevated in COPD patients, including leukocyte count, tumor necrosis factor (TNF)-α, soluble TNF-α receptors and lipopolysaccharide binding protein.[3-7] HMB has been suggested to improve immune function, especially under stressful conditions. It has been shown that HMB enhances lymphocyte blastogenesis in a dose-dependent manner in vitro.[16,23] HMB also has been shown to enhance nitrite production in macrophage and antibody production in animal studies.[24] Clark *et al*., also revealed that HMB supplementation resulted in higher CD3 and CD8 cells and lower human immunodeficiency virus (HIV) load in acquired immunodeficiency syndrome (AIDS) patients.[22]

Ten subjects (55.6%) in HMB group, compared to only 4 (25.0%) in the control group, showed improvement in pulmonary functions and moved closer to weaning from ventilators as they were changed to PSV or SIMV+ PSV mode. The percentage of improved subjects in the 2 groups may reach statistical significance had there been a larger sample size. PSV is one of the primary modes used for weaning from mechanical ventilation.[27] In this mode, the patient's spontaneous respiratory effort is augmented by additional pressure to promote the flow of air into the lung. The applied pressure level is held constant throughout the inspiratory phase. Only patients with reliable respiratory drive can be put on this mode. When a low level of applied pressure is successful, the patient is considered to be ready for weaning.[27] PSV is occasionally used in conjunction with SIMV to assure a preselected number of mandatory breaths in the event of apnea. A/C mode is mostly used when patients with normal respiratory drive but respiratory muscles are too weak to perform the task of breathing. PCV mode is predominantly used when patients show high airway pressure and poor oxygenation.[28] In this study, the ventilation mode of each patient was determined according to his/her physiological condition by physicians and respiratory technicians who were completely blind to the study to ensure the independent decision-making.

In this study, serum creatinine level was significantly decreased only after HMB supplementation. Blood urea nitrogen also showed a moderate decrease (P = 0.079) after the supplementation. These data suggested that HMB supplementation may have anticatabolic effect on protein metabolism in this group of COPD patients. The lack of significant change in P_I and P_E, indicators of respiratory muscle strength, may result from the short study period.

HMB has been suggested to enhance fat mass and muscular strength when used in combination with strength training.[17-19,21,29] HMB supplementation in untrained individuals, in combination with resistance training, has been shown to increase fat free mass and/or decrease markers of muscle breakdown, compared to placebo. Niessen *et al*., suggested that supplementation of 1.5 or 3 g/d HMB significantly reduced urinary 3-methylhistidine, a marker of muscle breakdown, in the first 2 weeks of resistance training in a dose-dependent manner.[17] In addition, Urine and plasma urea nitrogen were also decreased after 3 weeks of HMB supplementation and resistance training, suggesting a protein-sparing effect, in recreationally trained subjects.[19] Clark *et al*., suggested that supplementation of HMB, in combination with glutamine and arginine, for 8 weeks could increase fat free mass in AIDS patients and weight loss of more than 5% body weight in the past 3 months.[22]

Table 3. Modes of ventilator at baseline and after the 7-day study period in HMB and control groups (mean ± standard deviation)

Modes		Number of subjects	
Baseline	After	HMB	Control
PCV or A/C	PSV or SIMV+PSV	10 (55.6%)	4 (25.0%)
PSV or SIMV+PSV	PSV or SIMV+PSV	6 (33.3%)	9 (56.3%)
PCV	PCV	1 (5.6%)	3 (18.8%)
SIMV+PSV	A/C	1 (5.6%)	0 (0.0%)

PCV, pressure control ventilation; A/C, assist/control; PSV, pressure support ventilation; SIMV, synchronized intermittent mandatory

Supplementation of HMB may provide a better way to help these patients maintain adequate body weight, as even aggressive nutrition supplementations have mostly been ineffective.[30] HMB was converted to β-hydroxy-β-methyl-glutaryl-CoA (HMG-CoA), a precursor for cholesterol synthesis, in cytosol.[17] In muscle cells where the major supply of cholesterol comes from a de novo pathway, the increased cholesterol synthesis resulted from dietary supplementation of HMB may help the growth, production, or repair of the tissue in stressful or overload conditions.[17] This hypothesis is supported by the fact that several cholesterol synthesis inhibitors can cause severe myopathy.[31] In our study, the HMB group showed significant increase in plasma cholesterol after supplementation, indicating potentially elevated cholesterol synthesis.

Other proposed mechanisms of anticatabolic effects of HMB included modulation of hormonal receptor effects of cortisol, testosterone, growth hormone, insulin-like growth factor-1 (IGF-1), and enzymes responsible for muscle tissue breakdown.[18] However, urinary testosterone to epitestosterone ratio did not change after consumption of 3g HMB in healthy males.[32] IGF-1 and insulin levels also remained unchanged after HMB supplementation in lambs.[33] The detailed mechanism of HMB requires further research.

HMB at the doses of 3-6 g/d appeared to be well-tolerated in humans with no obvious adverse effect. Nissen *et al.*, reported a series of studies in healthy young and old subjects lasting from 3 to 8 weeks, in which the supplementation of 3 g HMB/d showed no adverse effect on psychological, blood chemistry, and hematology parameters.[34] At the consumption level of 3 and 6 g/d for 8 weeks, no adverse change was observed in blood glucose, urea nitrogen, hemoglobin, hepatic enzymes, lipid profile, leukocyte subpopulations, urine pH, glucose, and protein.[29] Total and LDL cholesterol were decreased in both studies,[29,34] suggesting potential health benefit and possible feedback inhibition of liver cholesterol synthesis in healthy subjects. No change in plasma lipid profiles, hepatic enzyme activities, and markers of kidney function was discovered in HIV-infected patients supplemented with HMB/glutamine/arginine complex.[22] A significant 6% decrease in total white blood cell was reported, with the major reductions in neutrophils and eosinophils.[16] However, Gallagher *et al*., revealed a significant increase in basophils after supplementation of 3g/d.[29] The physiological effect of the changes at these magnitudes was unclear. Our subjects did not show any signs of gastrointestinal complications during the HMB supplementation period. The blood analysis results did not show any adverse effect on HMB supplementation.

The subjects in this study were randomly assigned to HMB or control group on the alternative order of admission to ICU to prevent any bias in subject selection. Unexpectedly, a significant difference appeared in baseline body weight and BMI between the 2 groups. We used regression analysis to control baseline BMI in analyzing the magnitude of change between the 2 groups.

This short-term study suggested that HMB supplementation may have anti-inflammatory and anticatabolic effect and improve pulmonary function in COPD patients in an ICU setting. The small sample size may limit the statistical power as the differences in magnitude of change between the 2 groups were only moderately significant in white blood cell count and cholesterol and insignificant in CRP and creatinine after controlling for baseline BMI. Nevertheless, the changes in the HMB group indicated that there had been reduced inflammation and protein catabolism. The duration of this study may be too short to show significant improvement in respiratory muscle function. However, improved pulmonary function in the HMB group has been suggested according to the ventilator modes of the subjects. A long-term study with a larger sample size on the effects of HMB on muscle metabolism and physiological functions in patients with COPD or other muscle wasting diseases is warranted.

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Original Article

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短期補充β-hydroxy-β-methylbutyrate對加護病房的慢性阻塞性肺病病人的抗發炎及抗異化作用影響

發炎標記上升及肌肉耗損是慢性阻塞性肺病(COPD）的病人常見的問題。本研究的目的為研究7天的β-hydroxy-β-methylbutyrate（HMB）補充 對加 護病房 的COPD病人之發炎反應、蛋白質代謝及肺部功能的效應。34名需要使用呼吸機的COPD病人被隨機分配為HMB（n=18）或是控制組（n=16）。HMB組接受HMB每天3公克，共七天。在經過HMB的補充之後，病人的白血球計數、C反應蛋白及肌酸酐顯著的較低，而膽固醇及總蛋白質顯著的較高。兩組的體重則都沒有改變。10名HMB組（55.6％）及4名控制組（25.0％）的研究對象，從他們的呼吸器模式顯示出肺部功能有改善。這個短期的研究指出給予加護病房的COPD病人補充HMB，可能具有抗發炎及抗異化的作用並改善肺部功能。

關鍵字：β-hydroxy-βmethylbutyrate、發炎、C反應蛋白、慢性阻塞性肺病。