ERJ Express. Published on January 24, 2007 as doi: 10.1183/09031936.00073506

THE ROLE OF NEBULIZED BUDESONIDE IN THE TREATMENT OF EXACERBATIONS OF COPD

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ABSTRACT

Background: This study was designed to evaluate the hypothesis that nebulized budesonide (NB) might be an alternative to systemic corticosteroids (SC) in the treatment of patients with exacerbations of COPD (ECOPD).

Methods: Patients, hospitalized with ECOPD (n=159), were randomized into three groups. Group I received only standard bronchodilator treatment (SBDT), Group II received SC (40 mg prednisolon) plus SBDT, and Group III received NB (1500 mcg qid) plus SBDT. Improvement during 10-day hospitalization, and exacerbation and re-hospitalization rates after discharge were compared.

Results: While mean age was 64,1±8,9 years (F/M=0,1), mean FEV_1 at admission was found 37,2±12,2 % predicted. Arterial blood gases and spirograms recovered faster in Group II and III. While improvements in PaO_2 and FVC in Group II, and improvements in PaO_2, FVC and FEV_1 in Group III became significant at 24-hour control, first significant improvement in Group I appeared in SaO_2 at 72-hour control. Mean improvement in PaO_2 at 10-day were 9 and 8 mmHg higher in Group II and III respectively than Group I ($p<0,05$). Blood glucose demonstrated an upward trend only in Group II ($p<0,05$).

Conclusion: Our study demonstrates that NB may be an efficacious and safe alternative to SC in the treatment of ECOPD.

Systemic corticosteroids are strongly recommended in the management of exacerbations of chronic obstructive pulmonary disease (ECOPD) by all international guidelines (1,2). Despite its proven efficacy, there are still some drawbacks with respect to its acute and chronic adverse effects. Regarding that COPD patients are elderly and relatively immobilized, development of adverse effects due to systemic corticosteroid becomes a major concern. In the development of adverse effects like osteoporosis and bone fractures, thinning of the skin, posterior sub-capsular cataract formation, glucose intolerance and myopathy, cumulative systemic corticosteroid dose received is the most important parameter (3-6). It is well known that exacerbation rate is significantly higher in some COPD patients, and these patients need larger amounts of systemic corticosteroids for the control of exacerbations in a certain period of time (7,8). Hence, the risk for development of severe adverse effects due to repeated courses of systemic corticosteroid is much higher in this sub-group, and this condition led the clinicians to seek alternative options.

Nebulized corticosteroids have been available for the last decade. Since their topical anti-inflammatory activity is high, they are safely used as a substitute of inhaled corticosteroids in patients with stable COPD and bronchial asthma, where indicated. However, there are only a few studies in the literature related to their use in the management of exacerbations of bronchial asthma and COPD (9-14). The total daily dosages used in the relevant studies were ranging between 1 to 8 mg differing according to the methodology and the patient groups used in the studies. Preliminary data suggests that nebulized corticosteroids have the similar efficacy to systemic corticosteroids in the treatment of exacerbations of bronchial asthma and COPD.

Although the available data about the use of nebulized corticosteroids in ECOPD is giving a positive impression, this has yet to be explored with further studies. Accordingly, we designed this study to evaluate the safety and efficacy of nebulized budesonide suspension compared with systemic corticosteroid in the treatment of patients with ECOPD requiring hospitalization.

PATIENTS and METHODS

The study was conducted at Turgut Ozal Research Centre of Inonu University. The study protocol was approved by the ethics committee of the center. COPD patients who were hospitalized for an exacerbation were prospectively enrolled in the study. The informed consent was obtained from the all participants. The patients' diagnosis of COPD was made according to the criteria set by ATS (15). An exacerbation was defined as the presence of a

worsening in at least 2 of the following symptoms, cough, purulent sputum and dyspnea. The patients were hospitalized in cases when one or more of the following indications existed. These indications were severely increased symptoms, new onset of cyanosis and peripheral edema, confusion, lethargy, coma, use of accessory muscles for ventilation, significant comorbidities, failure to respond to initial treatment, the judgment that treatment at home to be insufficient, acidosis, persistent or worsening hypoxemia and/or severe or worsening hypercapnia and new onset arrhytmias. COPD patients hospitalized with specific reasons like pneumonia, pulmonary emboli, congestive heart failure and pneumothorax etc. as the cause of exacerbation were excluded. Only the patients with level II exacerbation was included in the study, and patients with risk of imminent respiratory failure requiring mechanical ventilation or direct admission to the ICU (level III exacerbation) were excluded (2). The patients who utilized systemic corticosteroids or had an exacerbation in the preceding month were not enrolled at all. The patients were registered in the study only once at the index hospitalization. ClinicalTrials.gov Identifier of the study is NCT00274222.

Treatments during hospitalization

The participants received identical treatment. To achieve administration of identical treatment arms, the patients were given same number of scheduled nebulized solutions everyday (eight times a day) and were infused single (50 ml) physiologic saline solution intravenously in the morning. The patients utilizing systemic corticosteroid received it in this solution, and addition of systemic corticosteroid did not have any effect on appearance of the solution. All nebulized solutions were delivered using the same type of nebulizer (Medel Aerofamily Jet Nebulizer, Polo di Torrile (PR), Italy). The medications were prepared outside the patients' rooms by a nurse, and the patients were not allowed to know which medications were delivered (or not) in nebulized forms and in intravenous solutions.

The patients were randomly allocated into three groups. The treatment groups are as follows;

Group I received bronchodilator treatment with nebulized salbutamol (2,5 mg qid) (Ventolin nebules, 2,5 mg/2,5 ml salbutamol, GlaxoSmithKline, Istanbul, Turkey), nebulized ipratropium bromide (0,5 mg qid) (Atrovent flakon, 0,5 mg/2ml ipratropium bromide, Boehringer Ingelheim, Istanbul, Turkey) in separate sessions. Their mini intravenous solution was infused as empty.

Group II received the same bronchodilator treatments as in Group I. Their mini intravenous solution included 40 mg prednisolone (Prednol-L ampul, 40 mg prednisolone, Mustafa Nevzat, Istanbul, Turkey).

Group III received combined form nebulized solution of salbutamol plus ipratropium bromide (qid) (Combivent flakon, ipratropium bromide 0,5 mg and salbutamol 2,5 mg/2,5 ml, Boehringer Ingelhaim, Istanbul, Turkey). This group of patients also utilized nebulized budesonide (1500 mcg qid) (Pulmicort nebulizer, 0,5 mg/2 ml budesonide, AstraZeneca, Istanbul, Turkey) The combined form of nebulized bronchodilator includes the same doses of salbutamol and ipratropium bromide as in Group I and II. This group received their infusion of mini intravenous solution as empty.

According to the study protocol, the patients could also utilize nebulized salbutamol as rescue medication. All patients were given supplemental oxygen and systemic methylxanthines, and antibiotics were used where signs of bacterial infection existed.

Treatments after Discharge:

The patients were hospitalized at least for 10 days, and received the treatment strictly as described above. After discharge, all patients were prescribed in a standard fashion with combined form of inhaled ipratropium bromide plus salbutamol (2 puffs qid) (Combivent aerosol, 20 mcg ipratropium bromide plus 100 mcg salbutamol in each puff, Boehringer Ingelheim, Istanbul, Turkey) and methylxanthines during one-month follow-up period. As rescue medication, they were allowed to use inhaled salbutamol (Ventolin Inhaler, 100 mcg salbutamol in each puff, GlaxoSmithKline, Istanbul, Turkey) outside the hospital. If discharged between 11 to 15 days, the patients in Group II and III completed the 15 day utilization of systemic or nebulised corticorticosteroids outside the hospital by using 32 mg of methylprednisolone tablets in the morning (Prednol tablet, 16 mg methylprednisolone in each tablet, Mustafa Nevzat, Istanbul, Turkey) or inhaled budesonide 1500 mcg qid respectively (Pulmicort turbuhaler, 100 mcg budesonide per dose, AstraZeneca, Istanbul, Turkey). Until 15 days of hospitalization, the initial treatment was not changed. If hospitalization period exceeds 15 days, both forms of corticosteroid preparations and infusion of physiologic saline solutions were discontinued.

Data Collection:

Complete blood counts, detailed biochemical analysis, spirometric measurements and arterial blood gas analysis were done at admission, 24, 72 hours, and 7 and 10 days. Besides, adverse effects developed, COPD deterioration, admission to the ICU, respiratory failure, patient's withdrawal of any reason, delayed discharge (beyond 15 days), in-hospital deaths, deaths after discharge within one month, exacerbation and re-hospitalization rates within one month after

discharge were recorded. Exacerbation after discharge was determined by using the definition as unscheduled visit to any medical unit due to increase in COPD symptoms like breathlessness, sputum production or cough. Patients' status after discharge was assessed by phone calls and home visits every week during one month period after discharge. Comorbidity was measured for all patients according to the model developed by Charlson et al . This index gives different scores for different chronic illnesses so as to predict mortality. In this method, severe diseases are assigned for higher scores, and milder diseases are given lower scores (congestive heart failure=1, malignancy=2, severe liver disease=3, AIDS=6, etc.) (16).

Measurements:

Spirometric examination at admission was done by using Vmax 20c spirometer (SensorMedics Corp., Yorba-Linda, California-USA). This test was performed in a standard fashion. The spirograms having the largest FEV_1 and FVC, selected among at least two technically acceptable spirometric measurements, were used in the analysis. Patients who missed more than one spirometric examination were excluded from the study.

Arterial blood gas analysis was performed while breathing room air at rest.

Statistical Analysis

Including the patients who might be censored during hospitalization period, a minimum sample size of 50 was required in order to obtain power reaching an acceptable level (80% power, α=0.05). We anticipated that we might have a dropout rate around 20% with this protocol. For comparison of changes in continues variables between and within the groups, analysis of variance and paired student-t tests were used respectively. The chi-square method was used to compare the number of patients in each group regarding the parameters related to the clinical indicators of treatment success including admission to the ICU, death, adverse events, and withdrawal of consent, deterioration of COPD, exacerbation rates and hospitalization rates after discharge. A two-sided P value < 0.05 was considered to be statistically significant.

RESULTS

Fifty-three patients were enrolled in each group. Data from 38 patients were not evaluated due to exclusion during the hospitalization period of the study, and 121 patients completed the study (Group I= 39, Group II= 40 and Group III= 42). The main reasons of exclusion were

inability to perform two consecutive spirometric examination (n=10), incompliance with the treatment (n=8), adverse effects (n=6), treatment failure or admission to the ICU (n=5), withdrawal of consent (n=5) and request for early discharge (n=4). The rates of dropouts were similar in three groups (26% in Group I, 24% in Group II and 21% in Group III). Further analysis of the groups according to the reasons of exclusion also revealed a similar distribution in each group. Antibiotics were prescribed for 59%, 63% and 57% of the patients in Group I, Group II and Group III respectively (p=0,882). General characteristics of the patients at admission who completed the study are presented in Table I. There was not any significant difference between the groups. Another 11 patients were lost to follow-up during one-month after-discharge period (4, 3 and 4 patients in Group I, II and III respectively), and one patient from Group I and II died during this period. Due to these, their follow-up data could not be evaluated.

Arterial blood gas analysis was performed in all patients, but initial spirograms could not be obtained in 20 patients; eleven due to lack of patient cooperation, nine due to technical problems. Although initial spirometric and arterial blood gas parameters were similar between the groups, absolute values at 10-day were better in Group II and III than in Group I. With regard to the absolute values of arterial blood gases and spirometric measurements at 10-day, mean FEF_{25-75} value in Group III was significantly higher than the values in Group I and II (p=0,03 and p=0,027 respectively). In addition to this, while direct comparison of arterial blood gases and spirometric parameters did not reveal any difference between Group I and II, FEV_1 value was also found significantly higher in Group III than Group I (p=0,004). When comparison was made between Groups I and III for absolute mean values of FVC and FEV_1/FVC, the trend was very close to the threshold value in favor of Group III (p=0,081 and p=0,077 respectively). In the same manner, comparison made for FEV_1 also revealed a similar trend between Groups II and III, in favor of Group III (p=0,057).

To better asses the response to the treatment, we also compared the improvement rates (difference between admission values and 10-day values) between different treatment arms. Among the parameters evaluated, improvement rates in SaO_2, PaO_2, FEV_1 and FVC were significantly higher in Group II and III than Group I. Mean improvement in PaO_2 at 10-day (final complete evaluation time) were 9 and 8 mm Hg higher in Group II (p=0,000) and III (p=0,009) respectively than in Group I (Table II). Similarly, higher improvement rates of 5,3% (p=0,022) and 5,9% (p=0,011) in SaO_2, of 10.6% (p=0,006) and 8.9% (p=0,007) in FVC and of 4.9% (p=0,038) and 7.2% (p=0,001) in FEV_1 were recorded in Group II and III respectively (Table II). The differences between Groups II and III were not statistically

significant, except the comparison of improvement rates in $PaCO_2$ (p=0,046). Mean improvement in $PaCO_2$ was found 3.9 mm Hg higher in group II than in Group III.

In the 24, 72 hours and 7 days intermediary periods, patients in Group II and III showed better recovery. Improvement rates in spirometric and arterial blood gas parameters at these periods are shown in Table II and Figure I and II. When compared to the initial values, first statistically significant improvement in Group I appeared in SaO_2 at 72-hour control (p=0,041). However, at 24-hour control, improvements in PaO_2 (p=0,038) and FVC (p=0,032) became statistically significant in Group II, and improvements in PaO_2 (p=0,03), FVC (p=0,024) and FEV_1 (p=0,014) became statistically significant in Group III (Table II). At the 7-day control, while all improvement rates in Group II and III, with regard to the spirometric (except FEF_{25-75} and FEV_1/FVC) and arterial blood gas parameters (except pH), reached a statistically significant level, improvements in FVC and PaO_2 in addition to FEF_{25-75} and FEV_1/FVC were not yet statistically significant in Group I (Table II). Between the groups and within the group comparisons for improvement rates in FEF_{25-75} did not yield any statistically significant result at any period. Later on, improvement rate in FEV_1/FVC became statistically significant at 10-day control only in Group III (p=0,019).

Detailed differential count of blood cells and measurements for biochemical parameters were done at the same periods with spirometric and arterial blood gas analysis. Except blood glucose level, there was no significant difference between the groups with respect to the hematological and biochemical parameters at admission, 24, 72 hours, 7 and 10 days (Table II). Absolute blood glucose level was found significantly higher in Group II than the glucose level in other Groups at 7 and 10-day measurements ($p<0,05$). In addition to this, while mean blood glucose levels were decreasing during hospitalization period in Group I and III, it was found higher than admission value in Group III at 7- and 10-day controls (Figure III).

An important primary endpoint in evaluating the efficacy of nebulized corticosteroids in our study was the number of patients with early and delayed discharge in the groups. As mentioned earlier, patients completed their 10-day controls at the hospital. Thus, the percentage of patients discharged at the 10^{th} day became 54%, 50% and 45% in Group I, II and III respectively (Table III). The delayed discharge (beyond 15 days) occurred in 10%, 10% and 7% in the relevant groups respectively (Table III). Percentages of the patients with early (relatively) and delayed discharge did not yield any statistically significant result between the groups.

Another primary endpoint was the attack rates and re-hospitalization rates within one month after discharge. Total numbers of exacerbations in Group I, II and III were 14, 8 and 9 times

respectively. These exacerbations resulted with hospitalization in 8, 4 and 5 times respectively during one month after discharge. Although there was an obvious trend towards the statistically significant site in favor of corticosteroid groups for both analyses, our results did not yield a statistically significant difference between the treatment arms.

DISCUSSION

In this study, we evaluated the short- and long-term efficacy and short-term safety of nebulized budesonide in the treatment of patients hospitalized with ECOPD. In the acute phase of the treatment, while recovery rates with regard to spirometric and arterial blood gas parameters did not differ between the groups utilizing systemic and nebulized forms of corticosteroids, the recovery rates were significantly better in the corticosteroid groups than the group receiving only bronchodilator treatment. In addition to these, blood glucose level showed a significant upward trend in patients treated with systemic corticosteroids.

Systemic corticosteroids are known to effectively improve the clinical parameters in ECOPD when compared with placebo (17-19). However, these effects are especially significant during short-term and are less obvious during follow-up (13). In our study we demonstrated that high dose nebulized budesonide may replace the systemic corticosteroid administration during hospitalization in patients with ECOPD, except very severe cases. All spirometric and arterial blood gas parameters improved in a similar rate in the both corticosteroid arms, and recovery of the patients on corticosteroids was better than the ones not receiving any corticosteroid. Moreover, analyses for the improvement rates in FEV_1 reached a statistically significant level faster in nebulized budesonide group, and the improvement in FEV_1/FVC became statistically significant only in nebulized budesonide group. Only the improvement in $PaCO_2$ in Group II was shown to be significantly higher than that in Group III at the end of 10-day period. However, this condition was probably due to almost significantly higher mean admission $PaCO_2$ level in Group II (p=0,077). Previous studies also reached more or less the same findings. Maltaise et al. demonstrated that the difference between the FEV_1 increases in systemic prednisolon (30 mg bid) and nebulized budesonide (2 mg qid) groups is only 60 ml over 3 days of their study ($p>0.05$) (13). Similarly, Morice et al. did not find any difference between the improvement rates of FEV_1 in the same groups over 5 days of the study (12). Their groups were administered 30 mg oral prednisolon versus 4 mg (2 mg bid) nebulized budesonide per day. Recently, Mirici et al. published a prospective randomized placebo-controlled study (14). Differing from the previous studies, their study design included arterial

blood gas parameters too, in addition to spirograms. They also did not show any significant difference between the improvement rates of the relevant parameters in their groups at the 30 minute, 6 hour, 24 hour, 48 hour and 10 day evaluations after hospitalization due to ECOPD. An important difference of our study from these pioneer ones is that we did not evaluate the very acute influence of corticosteroids on clinical parameters. Classically, appearance of anti-inflammatory effects of corticosteroids takes around 24 hours. Before this time, it is very difficult to attribute the recovery of clinical parameters to corticosteroids. At least differentiation of effects of rapidly acting bronchodilators from those of corticosteroids, if any, can not be made truly during first 24 hour. Moreover, previous investigators also stated that slight differences between the improvement rates in corticosteroid arms during the very acute phase could not be translated into any better final outcome (17,18). Due to these, we did not design our study in a way to evaluate the acute effects of corticosteroids. In our study, we used a similar dose of nebulized corticosteroid per patient with the previous studies. However, we believe that further studies are needed to assess whether lower doses could achieve equivalent efficacy or higher doses would be more beneficial.

To our knowledge, this is the first study evaluating the long term efficacy of nebulized budesonide in these patients. Our follow-up period was one month after discharge. We may receive criticisms for this duration claiming that this period could have been longer. However, it would be very difficult to speak about the influence of any type of corticosteroids on the relevant parameters beyond one-month period (20). After discharge, exacerbation rates and hospitalization rates have been the most important tools in the evaluating long term efficacy of any drug utilized in ECOPD. Although, there is not a perfect method to determine the true exacerbation rates, several investigators are working on it vigorously (7,8,21,22). As they also admitted, we know today that true exacerbation rates are much higher than expected, and the rates yielded by the previous studies are far from reflecting the true exacerbation rates. The main reasons underlying these facts are that COPD patients do not usually seek medical assistance for mild to moderate exacerbations and do not report such changes in their condition to the attending physician during follow-up. Thus, whatever precaution was taken, some of the attacks were missed and not recorded in the files. In our study, the criterion we used to assess the exacerbation rates was the unscheduled visits to any medical unit due to increased symptoms of COPD. Determining the re-hospitalization rates is relatively easier. Our methodology on this issue may also be criticized, but there is no better and practical approach. Besides, our missing rates for ECOPD, except mild attacks, and for re-hospitalization should be probably close to zero, because the patients were questioned once

every week during one-month after discharge period. Patients on corticosteroids revealed much better exacerbation and re-hospitalization rates, though not statistically significant. On the corticosteroid arms, these rates became almost half the rate in the only bronchodilator arm. Due to the limited number of patients in our study groups, the relevant scores did not reach the statistically significant level.

Due to the specific design of our study, length of hospital stay can not be directly used as a parameter in the comparison of our groups. Since patients were kept at the hospital at least for 10 days, we can only speak about percentage of the patients discharged at the 10^{th} day and about the patients with delayed discharge (after the 15^{th} day). From this specific point of view**,** we did not find an impact of corticosteroids on hospitalization period as it was the case in previous studies (13,17,18).

Adverse effects of the systemic corticosteroids are another important concern during the treatment of ECOPD. Even, administration of a single dose of systemic corticosteroids has been shown to increase the fracture risk in elderly patients with chronic lung disease as it is the case in COPD (21). However, total dose received in a life time (cumulative dose) is the most important determinant for the appearance of adverse effects due to utilization of systemic corticosteroids (6,13,23). As shown earlier, some patients with COPD undergo more frequent exacerbations, thus they receive higher amounts of systemic corticosteroids (7,8,20,22,24). Especially in these patients, the clinicians hesitate to prescribe systemic corticosteroids for every exacerbation. Since the systemic bioavailability of nebulized corticosteroids is almost negligible, development of systemic adverse effects are not expected practically. Adverse effects due to utilization of nebulized or inhaled corticosteroids are rather limited to their local effects like oropharyngeal candidiasis, hoarseness etc. From this point of view, frequent use of high dose nebulized budesonide seems to be virtually safe. But it should be kept in mind that, this issue has not been investigated at all. In our study too, neither any adverse effect directly due to its use was reported, nor there was difference between the groups with regard to percentages of patients who were excluded or withdrawn from the study of any reason. To better asses the effects of systemic and nebulized corticosteroids, we looked at many hematological and biochemical parameters in our study. Except blood glucose levels, we did not find any difference between the groups during the first 10 day after hospitalization. Initial blood glucose level was similar between the groups. But in the 7- and 10-day controls after hospitalization, it demonstrated an upwards trend in the group receiving systemic

corticosteroid while trend was downwards in the high dose nebulized budesonide group and the only bronchodilator group (Figure III).

In the original design of the present study, the evaluation of parameters like inspiratory capacity and important inflammatory markers in COPD like IL-8, TNFα, growth factors etc. were not included (25-28). We believe that future studies covering these parameters will enable the clinicians to understand the pathological mechanisms involved in COPD and to determine the efficacy of nebulized corticosteroids in a better way. Although dyspnea scales were utilized in measuring clinical response in some studies concerning the exacerbations, these scales (MMRC, Borg's category scale, visual analogue scale, BDI/TDI, dyspnea section of CRQ, etc.) have been traditionally utilized measuring dyspnea during stable period, during exercise and during shifting the treatment regimens. To our knowledge, there is not any standard/validated dyspnea scale in measuring dyspnea during exacerbations of COPD. The parameters we used in our study are basically objective ones, like arterial blood gases, spirometric measurements, haematological and biochemical analysis. Thus, the changes in their values during study period are virtually indicative of treatment response in different treatment arms. On the contrary, dyspnea measurement is quite subjective process, and changes in its rates stated by the patients may not be a reliable indicator particularly during an exacerbation. So we do not think that absence of dyspnea index in our study is a serious limitation and had important impact on our results. Although the size of our study population is rather large and more homogenous than the previous ones, we believe that this issue necessitates larger multicentric studies, preferably with the addition of a fourth arm of treatment including systemic prednisolone plus high dose nebulized corticosteroid to see the additive effect.

In summary, we found in our study that high dose nebulized budesonide is as efficacious as systemic corticosteroids in short- and long-term in the treatment of patients hospitalized with ECOPD, except very severe cases. In addition to this, nebulized budesonide exerted less systemic activity than systemic corticosteroid administration as indicated by serial blood glucose measurements. In conclusion, our data suggests that high dose nebulized budesonide may be an alternative to systemic corticosteroids in the treatment of ECOPD.

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Table I. General characteristics of the patients at admission.

	Group I (Only Bronchodilator) (n=39)	Group II (Systemic Corticosteroid) (n=40)	Group III (Nebulized Budesonide) (n=42)
Age (year)	63.5±10.1	64.9±7.1	63.9± 9.7
Gender (M/F)	35/4	33/7	35/7
Disease duration (year)	11.1±8.5	10.8±5.6	10.8±6.6
Smoking load (pack-years)	44.7±19.5	43.4±21.4	46.9±21.7
Current smokers (%)	44	45	50
Hematocrit (%)	49.0±6.1	48.9±5.8	48.2±6.5
Leucocyte count (10^9/L)	13355±5546	12715±5145	13605±5373
BUN (mg/dl)	21.9±9.4	24.9±13.1	20.9±8.8
Glucose (mg/dl)	114.0±31.7	116.4±37.8	114.3±24.9
FVC (%predicted)	64.5±21.5	57.5±17.7	64.3±20.4
FEV_1 (%predicted)	36.7±11.9	35.3±11.7	39.6±12.9
FEV_1/FVC	46.8±15.9	48.4±13.4	48.4±13.2
FEF_{25-75} (%predicted)	16.4±7.8	15.7±8.4	20.6±16.1
pH	7.41±0.09	7.41±0.08	7.41±0.09
SaO_2 (%)	83.6±10.0	80.1±12.4	79.9±13.7
PaO_2 (mm Hg)	52.4±11.1	49.1±12.6	50.1±14.8
$PaCO_2$ (mm Hg)	47.4±16.7	51.4±10.3	46.8±12.7
Comorbidity index	1.55±0.8	1.53±0.7	1.56±0.8

Table II. Patient characteristics at different follow-up times after hospitalization.

Characteristics	Groups	Baseline	At 24 hours	At 72 hours	On the 7th day	On the 10th day
FVC (%predicted)	Group I*	64.5±21.5	64.7±20.8	66.1±22.9	66.6±20	70.1±22.3
	Group II#	57.5±17.7	61.4±16.9	64.5±19.3	70.2±22.1	73.8±22.6
	Group III¶	64.3±20.4	68.7±21.6	70.0±19.7	75.5±23.9	78.8±21.8
FEV_1 (%predicted)	Group I	36.7±11.9	36.511.2	37.1±13.4	38.6±14.9	40.7±15.0
	Group II	35.3±11.7	36.4±12.8	38.4±15.3	42.913.9	44.2±14.6
	Group III	39.6±12.9	43.9±11.8	45.1±15.6	48.0±14.2	50.8±15.8
FEV_1/FVC	Group I	46.8±15.9	46.3±15.6	46.1±14.6	45.9±14.8	45.6±13.4
	Group II	48.4±13.4	47.5±12.1	48.4±13.7	48.1±11.9	47.5±11.7
	Group III	48.4±13.2	48.2±14.1	49.1±12.6	50.3±13.0	51.1±14.0
FEF_{25-75} (%predicted)	Group I	16.4±7.8	15.8±8.7	16.6±7.4	17.0±8.9	17.7±9.1
	Group II	15.7±8.4	15.9±9.3	16.4±10.4	16.6±9.9	17.4±10.0
	Group III	20.6±16.1	21.1±15.8	20.7±16.1	21.6±12.0	22.9±11.7
PaO_2 (mm Hg)	Group I	53.4±11.1	54.4±10.9	55.7±12.3	56.1±12.7	57.5±11.4
	Group II	49.1±12.6	54.7±10.3	59.5±11.8	60.6±13.3	62.5±12.3
	Group III	50.1±14.8	55.4±14.1	57.2±13.9	61.4±14.5	62.2±13.8
$PaCO_2$ (mm Hg)	Group I	47.4±16.7	47.1±15.4	46.2±11.9	43.5±10.7	43.9±9.8
	Group II	51.4±10.3	50.9±11.3	48.1±9.7	45.9± 10.0	45.2±9.8
	Group III	46.8±12.7	47.8±9.8	46.2±10.2	45.1±10.7	44.5±10.5
SaO_2 (%)	Group I	83.6±10.0	84.7±9.1	86.1±8.2	88.2±7.2	88.7±6.4
	Group II	80.1±12.4	82.2±10.1	85.4±9.7	88.9±7.1	90.5±6.8
	Group III	79.9±13.7	81.9±11.7	85.8±8.8	89.7±6.3	90.9±5.3
Glucose (mg/dL)	Group I	114.0±31.7	110.0±33.5	106.6±25.5	104.5±18.9	102.8±16.4
	Group II	126.4±37.8	114.9±35.1	112.3±29.8	127.1±27.7	129.1±23.4
	Group III	114.3±24.9	113.7±27.9	110.4±31.1	107.1±25.5	104.6±22.7

Table III. Percentage of the patients discharged at different times after hospitalization, and exacerbation and hospitalization rates after discharge.

Patients	Group I*(n=39)	Group II#(n=40)	Group III¶(n=42)
Patients discharged at the 10-day (%)	54	50	45
Patients discharged after15 days (%)	10	10	7
Exacerbation rates within 1 month after discharge	14	8	9
Re-hospitalization rates within 1 month after discharge	8	4	5

*The group receiving only bronchodilator treatment; #The group receiving systemic corticosteroid in addition to bronchodilator treatment; ¶The group receiving high-dose nebulized budesonide in addition to bronchodilator treatment.

Figure 1. Time-course of FEV_1 (% predicted) for three different groups after hospitalization.

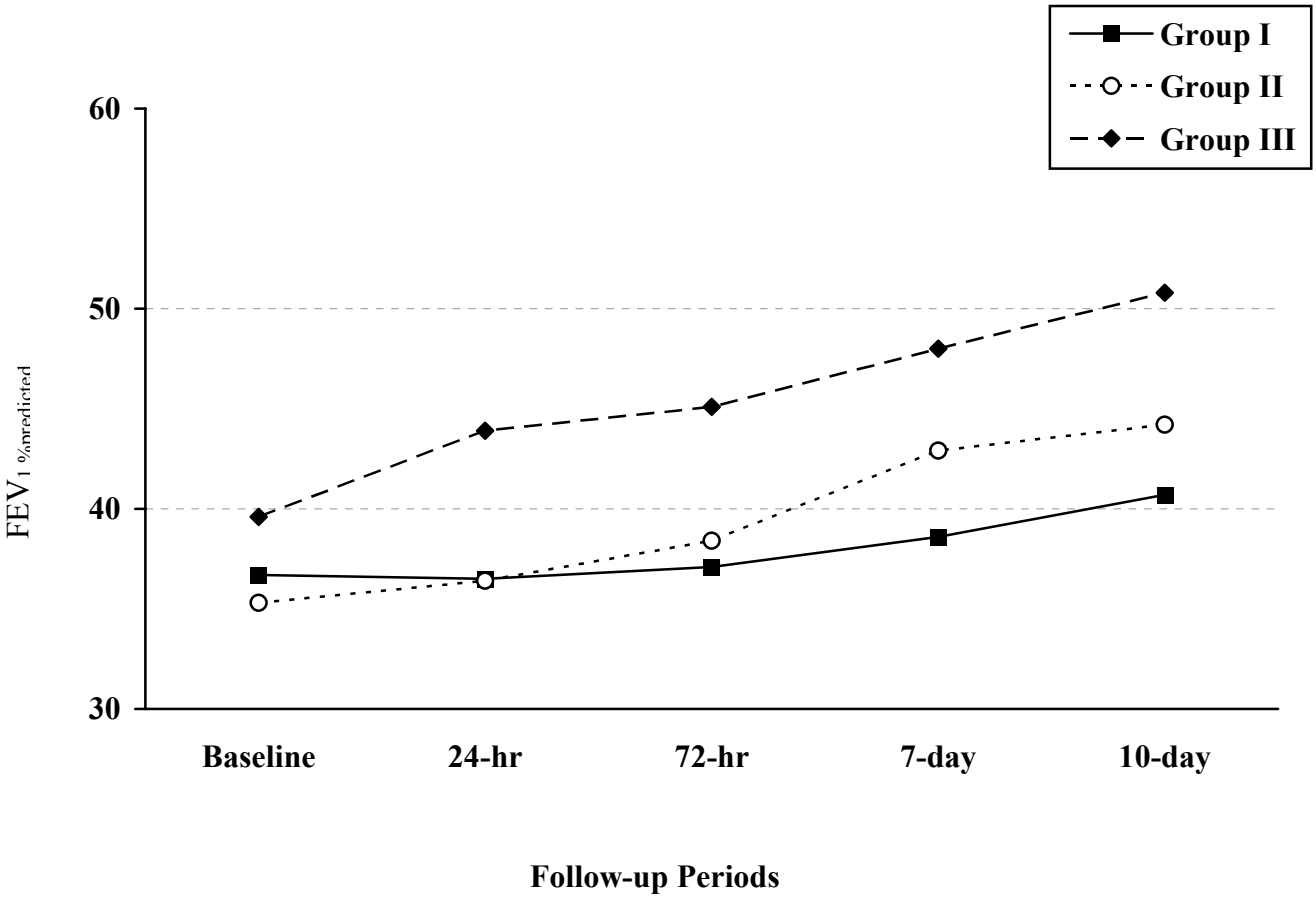

Figure 2. Time-course of PaO_2 (mm Hg) for three different groups after hospitalization.

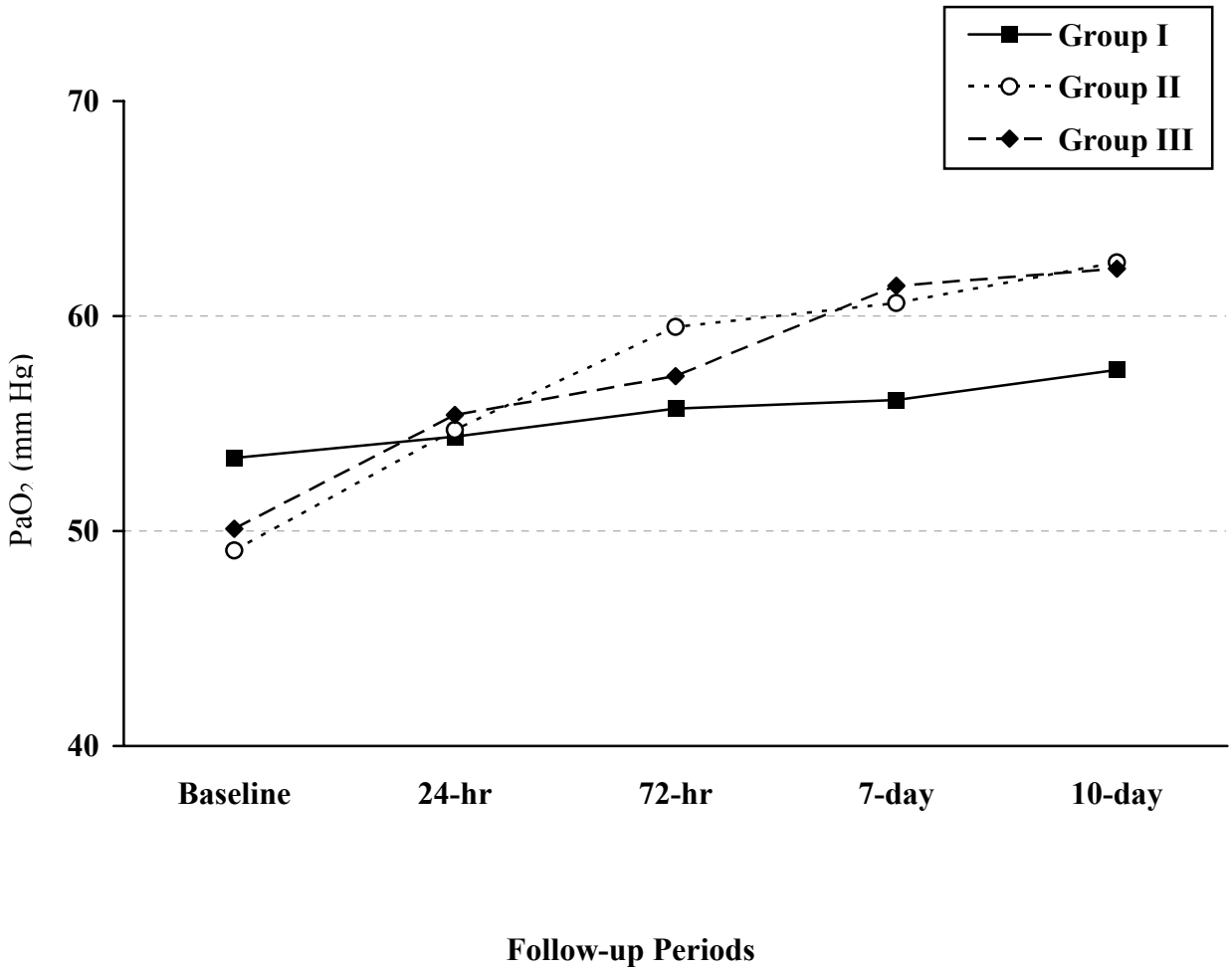

Figure 3. Time-course of blood glucose levels (mg/dL) for three different groups after hospitalization.