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Comparison of efficiency of inhaled and intravenous corticosteroid on pregnant women with COPD and the effects on the expression of PCT and hs-CRP

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Abstract. The efficiency of inhaled and systemic corticosteroids on pregnant women with chronic obstructive pulmonary disease (COPD) was investigated. The study also compared the effects of the administration on the expression of inflammatory mediator procalcitonin (PCT) and high-sensitivity C-reactive protein (hs-CRP). A total of 120 pregnant COPD patients were recruited and randomly allocated into the following three groups: Intravenous corticosteroid treatment group (n=42), inhaled corticosteroid treatment group (n=38), and control group (without any corticosteroid treatment, n=40). Patients of the all three groups received symptomatic supportive treatments including oxygen therapy, anti-infection therapy, expectorant, and bronchodilator. The serum PCT and hs-CRP expression levels were measured before treatment and after 7 days of treatment. Moreover, the clinical parameters such as symptoms, blood gas analysis parameters, pulmonary function indexes, fasting blood glucose (FBG) and adverse reactions were recorded. The overall clinical effective rates of the group received budesonide inhalation and the group receiving systemic methylprednisolone treatment were comparable. Both treatments were able to reduce the levels of inflammatory mediators, hs-CRP and PCT. On the other hand, treatments increased PaO_2 of arterial blood gas while reducing $PaCO_2$, thereby improving the lung function (FEV1% pred and FEV1/FVC) (P>0.05). The study observed that the FBG levels in COPD patients receiving systemic corticosteroid treatment were significantly increased, while budesonide inhalation did not significantly affect the FBG levels. In addition, rates of adverse events (such as mouth dry, oral ulcers, hoarseness) of systemic corticosteroid treatment group were significantly higher than those in inhaled corticosteroid treatment group and control group (38.1% vs. 17.5% vs. 5.0%, comparison between groups: P<0.05). In conclusion, inhaled and systemic use of corticosteroid both significantly improved dyspnea and other clinical symptoms of pregnant COPD patients by increasing oxygen partial pressure, correcting hypoxemia, and enhancing lung function. Moreover, fewer adverse reactions were observed with inhaled corticosteroid treatment, suggesting that inhaled administration is a relatively good, safe and effective treatment for pregnant COPD patients.

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Key words: chronic obstructive pulmonary disease, pregnancy, corticosteroid, inhalation, PCT, hs-CRP

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized with pathological features of inflammatory changes such as epithelial hyperplasia, hypertrophy of airway mucosa, and clinical manifestation of partially reversible airflow obstruction. The prime cause of COPD is smoke either primary or secondary (1). Moreover, smoke in the environment is also responsible to a great extent for the spread of COPD especially in females (2). Clinically, COPD patients often experience continuous deterioration due to the recurrence of re-infection symptoms, which has become an important reason for increased mortality (3,4). Corticosteroid used as anti-inflammatory agent and vasoconstrictor of small arteries could reduce inflammatory exudation and reduce airway obstruction, enabling its wide application in COPD treatment. However, long-term systemic therapy is likely to pose severe adverse effects on human body. Changes in physiological and endocrine structure accompanied with suppression of cellular immune function during pregnancy further increase the susceptibility to infection. According to the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD, version 2009), inhaled steroid medicines are recommended for AECOPD (acute exacerbations of chronic obstructive pulmonary disease) patients failed to achieve satisfactory outcomes with bronchodilators or hospitalized AECOPD patients (5). In the present study, 120 pregnant women with COPD admitted to the Department of Intensive Care Union, of The First People's Hospital of Xuzhou (Xuzhou, China) from April, 2015 to May, 2016 were recruited to compare the clinical efficiency and adverse events during treatment with systemic corticosteroids and topical inhaled corticosteroids. The above tasks were performed by evaluating the effects of different approaches on inflammatory factors such as procalcitonin (PCT) and high-sensitivity C-reactive

protein (hs-CRP), so as to provide more appropriate, safe and effective treatment plan for pregnant COPD patients.

Materials and methods

General materials. One hundred and twenty pregnant women with COPD aged 25-48 years were recruited. Patients were admitted to the Obstetrics and Gynecology Department of The First People's Hospital of Xuzhou from April 2015 to May 2016 and signed written informed consent before initialization of the study. Further, the Ethics Committee of The First People's Hospital of Xuzhou provided ethical clearance for the present study. COPD was diagnosed with the FEV1/FVC ratio (the ratio of the forced expiratory volume in the first one second to the forced vital capacity of the lungs) after inhalation of bronchodilator <70% (6). Patients with one or more conditions listed in the exclusion criteria were excluded (7): Severe heart failure and hepatic and renal dysfunction; other existing lung diseases; metabolic disorders and consumptive diseases, such as hyperthyroidism, cancer, diabetes mellitus, and active tuberculosis; impaired consciousness.

Experimental methods. Recruited patients conforming to the inclusion criteria were randomly allocated into three groups: Intravenous corticosteroid treatment group (n=42), treated with methylprednisolone (cat. no. MB0668; Pharmacia and Upjohn Co., Pfizer, NY, USA) 40 mg, OD, for 7 days; inhaled corticosteroid treatment group (n=38), treated with budesonide aerosol (cat. no. H20140511; AstraZeneca AB, Södertälje, Sweden), 2 mg, tid, for 7 days; and control group receiving no corticosteroid treatment. Patients in all groups received routine symptomatic supportive care, including continuous low flow oxygen inhalation, anticholinergic medications and theophylline bronchodilator, and antibiotics treatment. Gestational weeks and ages were comparable among patients in the three groups.

Parameter detection. The serum PCT and hs-CRP expression levels were measured before treatment and after 7 days of treatment. Further, the clinical parameters such as symptoms, blood gas analysis parameters, pulmonary function indexes, fasting blood glucose (FBG) and adverse reactions were recorded.

Measurement of arterial blood gas parameter oxygen partial pressure (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$): The arterial blood gas analysis was performed with blood gas analyzer I-STST1 (300) mode (Abbott Pharmaceutical Co. Ltd., Lake Bluff, IL, USA).

Pulmonary function test: Spirometry (BTL-08, BTL Group Ltd., London, UK) was applied to measure the FEV1% pred (predicted % forced expiratory volume in 1 min) and FEV1/FVC.

PCT and hs-CRP measurement: PCT was measured using double antibody sandwich immunochromatography Lumat LB 9507 PCT-Analyzer (Berthold Technologies GmbH & Co. KG, Bad wildbad, Germany); and hs-CRP was measured with turbidimetric immunoassay (QuikRead, Espoo, Finland).

Determination of clinical efficiency. The clinical efficiency was measured as 'ineffective', 'effective', and 'significantly effective' based on the frequency of coughs, the amount of sputum, the degree of dyspnea, and the auscultation of the lungs (8). The overall efficiency rate was calculated with the following formula: (significantly effective cases + effective cases)/total number of cases x 100%.

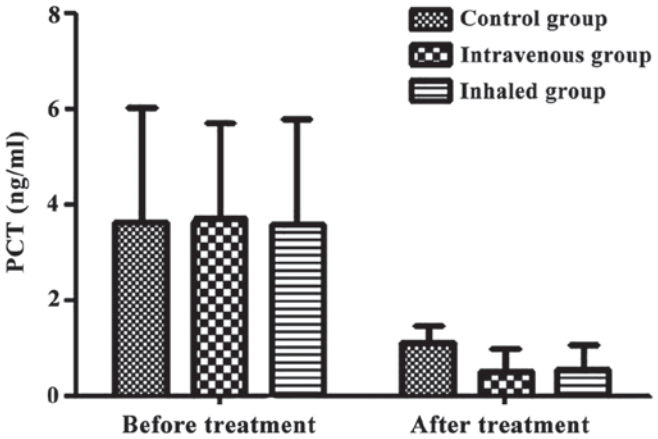

Figure 1. PCT level change of varying groups before and after treatment. The hs-CRP levels of all three groups are significantly decreased compared with pre-therapy conditions (P<0.05). The downregulation of inhaled and intravenous corticosteroid treatment groups is significant compared to the control group (P<0.05). However, comparing inhaled and intravenous corticosteroid treatment groups no significant difference was observed.

Statistical analysis. SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA) was used to analyze the data. Quantitative data were described as mean ± standard deviation, and assessed using F-test. Enumeration data were expressed as percentages (%) and performed with Chi-square test to compare the difference. P<0.05 was considered to indicate a statistically significant difference.

Results

No statistically significant differences were observed by comparing parameters including age, gestational weeks, lung function, blood gas analysis, inflammatory factors (PCT, hs-CRP) and FBG among different groups.

Results of blood gas analysis. The rates of improvement of blood gas analysis (pH, PaO_2, $PaCO_2$) of the inhaled corticosteroid treatment group and intravenous corticosteroid treatment group were both significantly higher than those in the control group (P<0.05; Table I).

Pulmonary function indicators. The pulmonary function indicators (FEV1% pred, FEV1/FVC) of inhalation treatment group and intravenous treatment group increased from (42.42±3.29, 47.49±3.55) and (42.22±3.57, 47.35±3.68) to (50.65±3.57, 54.79±3.44) and (49.47±3.37, 53.76±3.15), respectively. Both were significantly higher than that of the control group (P<0.05; Table II).

Change in PCT levels. The PCT values before and after treatment of the control group, intravenous treatment group and inhalation treatment were 3.64±2.37 vs. 1.10±0.35 ng/ml,

Table I. Blood gas analysis among the three groups of patients (mean ± SD).

Parameters	Control group (n=40)	Intravenous treatment group (n=42)	Inhalation treatment group (n=38)	F/χ^2 value	P-value
$PaCO_2$ (mmHg)					
Before treatment	42.98±3.77	43.25±4.15	41.53±4.56	0.333	0.836
After treatment	40.44±2.86[a,c]	37.96±2.96[a,b]	38.83±3.55[c]	4.997	0.023
PaO_2 (mmHg)					
Before treatment	60.68±3.69	59.98±4.03	61.05±4.92	0.579	0.566
After treatment	63.62±3.48[a,c]	66.83±3.14[a,b]	66.55±3.36[a,b]	2.632	0.039
pH					
Before treatment	7.30±0.04	7.32±0.04	7.33±0.03	0.848	0.347
After treatment	7.36±0.03[a,c]	7.38±0.04[a,b]	7.40±0.03[c]	4.580	0.021

[a]P<0.05, [b]P<0.05, and [c]P<0.05 correspond to comparison with pre-therapy value of the same group, comparison with post-therapy value of the control group, and comparison with post-therapy value of intravenous treatment group.

Table II. Comparison of pulmonary function indicators among patients of three groups (mean ± SD).

Parameters	Control group (n=40)	Intravenous treatment group (n=42)	Inhalation treatment group (n=38)	F/χ^2 value	P-value
FEV1% (pred)					
Before treatment	42.41±3.29	42.22±3.57	42.42±3.29	0.287	0.919
After treatment	44.35±2.65[a,c]	49.47±3.37[a,b]	50.65±3.57[a,b]	3.192	0.023
FEV1/FVC (%)					
Before treatment	47.8±2.68	47.35±3.68	47.49±3.55	0.301	0.819
After treatment	50.43±3.02[a,c]	53.76±3.15[a,b]	54.79±3.44[a,b]	2.998	0.040

[a]P<0.05, [b]P<0.05, and [c]P<0.05 correspond to comparison with pre-therapy value of the same group, comparison with post-therapy value of the control group, and comparison with post-therapy value of intravenous treatment group.

3.71±1.99 vs. 0.50±0.49 ng/ml, and 3.58±2.20 vs. 0.56±0.49 ng/ml, respectively. It was noted that the inhibition of inflammatory mediator PCT in corticosteroid-treated group was remarkably enhanced in comparison to that of the control group (P<0.05; Fig. 1).

Change in hs-CRP level. The hs-CRP levels before and after treatment of the control group, intravenous treatment group, and inhalation treatment were 70.12±36.68 vs. 25.06±6.66 mg/dl, 68.87±36.01 vs. 15.97±5.99 mg/dl, 73.68±37.96 vs. 14.47±5.78 mg/dl. The inhibition level of inflammatory mediator hs-CRP in corticosteroid-treated group was remarkably enhanced compared with that of the control group (P<0.05; Fig. 2).

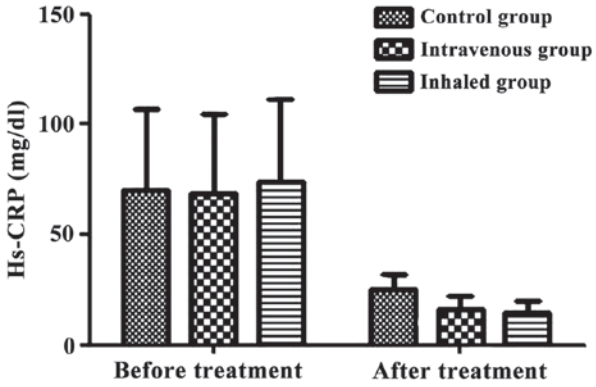

Figure 2. Hs-CRP level change of varying groups before and after treatment. The hs-CRP levels of all three groups were significantly decreased compared with pre-therapy condition (P<0.05). The downregulation of inhaled and intravenous corticosteroid treatment groups was significant compared to the control group (P<0.05). However, comparing inhaled and intravenous corticosteroid treatment groups no significant difference was observed.

Change in FBG level. Compared with the control group and inhaled corticosteroid treatment group, the FBG level of intravenous corticosteroid treatment group increased significantly (P<0.05) (Table III).

Comparisons of rates of clinical efficiency and adverse events. The overall clinical efficiency rates of inhaled and intravenous corticosteroid treatment groups were comparable (P>0.05), and both were higher than that of the control group (P<0.05).

Table III. Comparison of fasting blood glucose among three groups of patients (mean ± SD).

Observation index	Control group (n=40)	Intravenous treatment group (n=42)	Inhalation treatment group (n=38)	F/χ^2 value	P-value
FBG (nnmol/l)					
Before treatment	4.92±0.49	4.96±0.55	4.85±0.53	0.431	0.617
After treatment	5.01±0.46[c]	5.64±0.56[a,b]	5.03±0.45[c]	7.393	0.009

[a]P<0.05, [b]P<0.05, and [c]P<0.05 correspond to comparison with pre-therapy value of the same group, comparison with post-therapy value of the control group, and comparison with post-therapy value of intravenous treatment group.

Table IV. Comparisons of rates of clinical efficiency and adverse events among three groups of patients.

Observation index	Control group (n=40)	Intravenous treatment group (n=42)	Inhalation treatment group (n=38)	F/χ^2 value	P-value
Overall efficiency rate [n (%)]	26 (65.0)	38 (90.5)[a]	35 (87.5)[a]	14.577	0.003
Adverse events [n (%)]	2 (5.0)[b]	16 (38.1)[a]	7 (17.5)[a,b]	15.203	0.004

[a]P<0.05 and [b]P<0.05 correspond to comparison with post-therapy value of the control group, and comparison with post-therapy value of intravenous treatment group.

Overall rates of adverse events of inhaled and intravenous corticosteroid treatment group (such as mouth dry, oral ulcers, hoarseness) were significantly higher than that of the control group, and the increase was more pronounced in the intravenous corticosteroid treatment group (P<0.05; Table IV).

Discussion

Comprehensive treatment approaches for acute exacerbation of COPD (AECOPD) mainly include bronchial dilation, anti-inflammatory therapy, and use of corticosteroids to control airway inflammation (9). Studies have shown that systemic corticosteroid treatment helps shorten the rehabilitation time, restored lung function and improved hypoxemia. Further, it also reduced hospital stay and early recurrence rate. However, multiple adverse events could be induced by corticosteroid treatment. This included abnormal lipid metabolism, blood sugar disturbance, and infection secondary to immune function decline. Moreover, in a few cases, patients might also experience respiratory failure (10,11). With local administration of corticosteroid via inhalation, drugs are inhaled through the airway into the alveolar, where the highly concentrated local drug deposition on the lesion surface directly exerts the therapeutic effect. The hepatic first-pass metabolism of systemic administration can be avoided, thus significantly reducing the side effects. However, whether the inhaled corticosteroid could replace the systemic administration or existence of any potential difference when compared with systemic corticosteroid therapy remained a matter of concern.

COPD patients experience persistent airflow obstruction. Acid-base and electrolyte disorders could be detected on the basis of blood gas analysis (pH, $PaCO_2$ and PaO_2), This helped to diagnose potential hypoxemia or hypercapnia and types of respiratory failure, and predict the outcome. Around half of AECOPDs could be attributed to bacterial infection-relevant cause (12). As an acute-phase protein increasing in positive proportion to infection severity in early onset of infection, CRP level is insensitive to treatments such as corticosteroid, immunosuppressive agents, and anti-inflammatory drugs. This enabled CRP as a major indicator for early diagnosis of COPD and reflector of clinical treatment outcome (13,14). PCT is the precursor of calcitonin and significantly increases only during bacterial infection. It is currently considered that the sensitivity and specificity of serum PCT in the diagnosis of bacterial inflammation are significantly better than those of CRP (15,16). Recent findings showed that treatment course of patients with respiratory tract infection receiving PCT-based antibiotic therapy is significantly reduced when compared with patients receiving treatment guided otherwise. Further, 30-days follow-up did not show any adverse event, suggesting that PCT could be used as satisfactory supplementary evidence for diagnosis of AECOPD (17,18). In the present study, under the same treatment time, there was no significant difference in the overall rate of clinical efficiency between the inhaled budesonide treatment group and the systemic methylprednisolone treatment group. Both resulted in the decrease of inflammatory mediators (hs-CRP and PCT). The PCT levels before and after treatment of the control group, intravenous corticosteroid treatment group and inhaled corticosteroid treatment group were 3.64±2.37 vs. 1.10±0.35 ng/ml, 3.71±1.99 vs. 0.50±0.49 ng/ml and 58±2.20 vs. 0.56±0.49 ng/ml, and accordingly the hs-CRP levels before and after treatment were 70.12±36.68 vs. 25.06±6.66 mg/dl, 68.87±36.01 vs. 15.97±5.99 mg/dl and 73.68±37.96 vs. 14.47±5.78 mg/dl, respectively. Combination of increase in arterial blood gas PaO_2 and decrease in $PaCO_2$, in addition to improvement of lung function indicators FEV1% pred and FEV1/FVC suggested that, local inhalation and intravenous systemic corticosteroid treatment could help in the reduction of

the inflammatory response, hypoxia, and effectively improve lung function.

Corticosteroid treatment during COPD acute exacerbation could improve rate of clinical efficiency and reduce hospital stay by improving FEV1 and increasing PaO_2 (10,19,20). Budesonide given with oxygen-driven atomization device enters lung via airway and acts on lung tissue cells and exerts local anti-inflammatory and antiallergic effect with high selectivity. However, some patients might experience adverse events including dry mouth, throat soreness, hoarseness and oral candidiasis. Corticosteroid provides efficiency by generating active complex by binding with cytoplasm and hormone receptor on the cell membrane to promote apoptosis of inflammatory cells. It has been reported to reduce airway hyperresponsiveness, and relieve bronchospasm and improve dyspnea (21). In the present study, we found that the fasting blood glucose (FBG) level of COPD patients receiving systemic corticosteroid treatment was significantly increased, while inhaled budesonide did not affect FBG. In addition, we observed that incidence of adverse events such as dry mouth, oral ulcers, and hoarseness of systemic corticosteroid treatment group was higher than local aerosol inhalation treatment group and control group. The difference might be attributed to the fact that inhaled corticosteroid generated high local concentration of drugs, leaving low amount of drugs into systemic circulation. Therefore no obvious systemic biological effect was observed without increase of blood sugar levels due to liver glycogen gluconeogenesis, and the adverse events were relatively relieved as well.

The approach, dosage and course of clinical application of corticosteroid should be determined by selecting individualized protocol based on varying patient population and disease condition. Considering that the recruited patients in the study were pregnant women, the side effects secondary to systemic corticosteroid use might exceed the therapeutic effectiveness. Therefore, in summary, topical aerosol inhalation is an ideal administration approach, which might be more suitable for pregnant COPD patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YZ contributed significantly to writing the manuscript and detectin serum PCT and hs-CRP expression levels. FL and YL analyzed and interpreted clinical parameters.YS measured arterial blood gas parameter. ZL and GC performed clinical efficiency. WZ provided statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of The First People's Hospital of Xuzhou (Xuzhou, China). Written informed consents were signed by the patients and/or guardians.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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