Comparison of the effect of Pulmicort and Systemic Corticosteroid on the Treatment of patients with Acute Obstructive Pulmonary Attack Referring to the Emergency Department

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ABSTRACT

Background: The aim of this study was to compare the effect of pulmicort and systemic corticosteroids on the treatment of patients with acute obstructive pulmonary attack (AOPA) by controlling confounding factors (age and sex).

Methods: This study was a double-blind clinical trial performed on 72 patients with AOPA in Besat Hospital, Tehran, Iran from 20 March 2016 to 20 March 2017. Patients were randomly assigned into two treatment groups of nebulized pulmicort (budesonide) or systemic corticosteroids using prednisolone 50 mg or hydrocortisone 200 mg. To test the main hypothesis of the research, logistic regression analyzes were performed while Chi-square and Fisher exact tests were used to tests the sub-hypotheses of the study in SPSS 21.

Results: The odds of recovery in patients who received pulmicort was 6.68 times higher than the systemic corticosteroids treatment group (Odds ratio (OR) = 6.68, P-value = 0.003). The odds of recovery in women was 11.48 times higher than men (OR = 11.48, P-value = 0.003). 0.94 odds of recovery in older aged patients compared with lower ages showed that the chance of remission reduces with aging. (OR = 0.94, P-value = 0.002). According to 2 independent sample t-test, the difference in pt recovery on the basis of age was significant only in the patient who received pulmicort.

Conclusion: Based on the results of this study, pulmicort was more effective than systemic corticosteroid in the treatment of patients with AOPA regardless of their gender.

Keywords: Acute obstructive pulmonary attack, Pulmicort, Systemic corticosteroid

INTRODUCTION

Today, lung diseases have become more prevalent due to lifestyle, increased smoking, environmental pollution, and adverse occupational and industrial exposures1. Pulmonary obstruction diseases are a kind of respiratory diseases that are associated with airway obstruction2. Pulmonary obstruction diseases include chronic obstructive pulmonary disease (COPD), asthma, emphysema and bronchitis3. COPD is a set of physiological disorders4. This disease which is serious and disabling5 is characterized by progressive limitation in the airflow of the lungs and an abnormal inflammatory response to noxious stimuli6. In 1990 COPD was known as the sixth leading cause of death worldwide which will be the third in 2020. Based on the report of World Health Organization (WHO), COPD was responsible for 6% of all deaths globally in 2012. Destroyed years of life due to disability caused by illness or through early mortality along with high death rates and burdening significant cost to health systems are most harmful consequences of COPD7. The results of an analysis of mortality dynamics in the USA showed that when most causes of deaths were dropped between 1969 and 2013, no reduction was occurred in terms of COPD (8). Pulmonary emphysema is an anatomical diagnosis9 characterized by loss of both matrix and cellular elements of the lung due to damage to the lung parenchyma which lead to the enlargement of the alveolar spaces and thus impairing gas exchange between the alveolar space and the capillary blood10,11. It usually occurs in adults and between the ages of 55-75 and is more common in men than in women12. Inflammation of the airways between the nose and the lungs is called bronchitis, which can be acute or chronic. The first sign of chronic bronchitis is a mild cough called smokers' cough13. Asthma is one of the most common diseases of childhood and a type of chronic and progressive obstruction of respiratory tract that affects one in ten children, so that approximately 80% of cases of asthma have been reported before the age of 6 years14. One of the medications used in long-term management of obstructive pulmonary diseases is the inhaled form of budesonide (pulmicort) which is a corticosteroid that

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ORIGINAL ARTICLE

P J M H S Vol. 12, NO. 1, JAN – MAR 2018 529
is also available in the forms of tablet, nasal spray and rectum\textsuperscript{15,16,17}. The drug was initially registered in 1973 and its commercial use began as an asthma drug in 1981 and was put on the WHO list as one of the essential, effective and safe medicines needed in the health system. In the inhaled form of budesonide, common side effects include respiratory infections, cough and headache and in the form of tablets, it includes tiredness, vomiting and joint pain. Its serious side effects include increased risk of infection, loss of bone strength and cataracts\textsuperscript{18,19}. Pulmonary medicine delivery has attracted many scientific and medical attention in recent years and many improvements have been made in the local treatment of pulmonary diseases by increasing local attachment and reducing systemic complications due to prescribing low dose of medications\textsuperscript{20}.

Considering the importance and high prevalence of pulmonary obstruction diseases, this study was designed to compare the effect of pulmicort and systemic corticosteroids on the treatment of patients with AOPA referring to the emergency department to provide the necessary evidence to decide on choosing a better, safer, and more cost effective drug for patients with AOPA.

METHODS

Study characteristics and patients: This double-blind clinical trial study was conducted at a tertiary teaching hospital, Besat, Tehran, Iran from 20 March 2016 to 20 March 2017. The study population were patients with acute attack of obstructive pulmonary admitted to the emergency department. Patients with respiratory distress accompanied by wheezing, asthma attack, and acute exacerbation of chronic obstructive pulmonary disease were included in the study, while pulmonary embolism, pneumonia, and reluctance of patients to participate in the study were exclusion criteria of this research.

Sample Size: According to the study conducted by Singhi et al\textsuperscript{21} and with respect to the following expression, a total of 72 patients in two groups of 36 subjects were enrolled in the study:

\[ H^2 - 1 = \frac{1}{12} n \left( \mu_1 - \mu_2 \right)^2 \]

where \( H^2 \) is the prevalence, \( n \) is the sample size, \( \mu_1 \) and \( \mu_2 \) are the means of the two groups. Alpha and beta are the first and second types of errors of the study, respectively. P1 and P2 are the efficacy of pulmicort and systemic corticosteroid, respectively.

Randomization and blinding: Without distinguishing between patients who had entered the study, they were assigned to the pulmicort or systemic corticosteroid treatment groups using unbiased coins. Therefore, the allocation of patients to the two groups was completely randomized. In this study, the subjects under study and the treatment team, both were unaware of the contents of the medications.

After completing the study and collecting the results, the codes for each patient were provided to the research team.

Treatments: The patients allocated to the pulmicort group received drug in nebulized form for 10 minutes and also twice in half an hour at a dose of 1 mg, while patients of the systemic corticosteroids group received prednisolone 50 mg (all drug in 1 time) or hydrocortisone 200 mg (depending on the patient’s condition or severity of the vital signs that patient was able to swallow pills conveniently or not). Moreover, standard treatment of acute attack of obstructive pulmonary using beta-agonists was also performed in patients. Peak flow measurement was conducted before and after the start of treatment for all patients and values of forced expiratory volumes after 1 second (FEV1) were also recorded.

Analysis: Both descriptive and inferential statistics were used to analyze the data in this study. To describe age variable, bar graph and indexes of central tendency and dispersion were used. Chi-square and logistic regression analysis was employed to compare the improvement of patients between the two groups. All analyzes were performed using SPSS software version 21. Excel 2013 software was used to plot statistical charts.

Ethical Considerations: A written, informed consent was received from each of the patients and the study protocol was approved by Ethics Committees of both AJA University of Medical Sciences and Besat Hospital. Patients were assured that their information will remain confidential and their names will not be disclosed. This right was given to the patients to cut off their cooperation at each stage of the research for any reason or even without any definite cause.

RESULTS

Demographic characteristics: There were 20 females (55.6%) and 16 males (44.4%) in the group of patients who received pulmicort while systemic corticosteroid group was consisted of 21 females (58.3%) and 15 (41.7%) males. Table 1 explains the statistical indicators corresponding to the age of the subjects of the research. Figure 1 shows the age distribution of study patients. The youngest and oldest patients in the pulmicort group were 39 and 61 years old, respectively. The age range of patients in the systemic corticosteroid group was 40 to 61 years. These results show that the baseline demographic characteristics between the two treatment groups were similar.

Analytical statistics: Main hypothesis: The effect of pulmicort and systemic corticosteroid differs in the treatment of patients with AOPA by controlling the confounding factors (age and sex).
To investigate the main hypothesis of the research, logistic regression test was used. At first, Hosmer-Lemeshow test was used to evaluate the fit of the logistic regression model. The result suggested the goodness of the fit of the model (Chi-square=4.018, P-value=0.855). Model justification with available variables was 49%. Table 2 shows the effectiveness of drugs on disease with control of gender and age variables. Based on the regression analysis results presented in Table 2, the odds of recovery were higher in pulmicort receivers, in women, and in lower ages compared with systemic corticosteroids receivers, men and older ages.

Sub-hypotheses (1): The effect of pulmicort and systemic corticosteroid differs in the treatment of patients with AOPA.

To test this hypothesis, the Chi-square test was used and its results are presented in Table 3. It was found that 19(52.8%) patients of whom received systemic corticosteroid recovered their health, while pulmicort was effective for 28(77.8%) patients of whom received this treatment. This difference was significant at 5% error level. Sub-hypotheses (2): The effect of pulmicort and systemic corticosteroid differs in the treatment of patients with AOPA based on their gender. To test this hypothesis, Chi-square test as well as Fisher’s exact test were used and the results are presented in Table 4. In the group of patients receiving systemic corticosteroids, the number of improved men and women was 5(31.2%) and 14(70%) respectively. This difference was statistically significant at 5% error level. Also, the difference in drug efficacy between men and women who received pulmicort medication was also significant at 5% error rate. It was observed that 53.3% of men (n=8) and 95.2% of women (n=20) of this treatment group recovered their health after the intervention.

Sub-hypotheses (3): The effect of pulmicort and systemic corticosteroid differs in the treatment of patients with AOPA based on their age.

To investigate this hypothesis, two independent sample t-test was employed (Table 5). It should be noted that the normality test of the age distribution of patients that was first evaluated by Kolmogrov-Smirnov test, indicated that the distribution was normal (ZK-S=0.822, P-value=0.590). In the corticosteroid group, although the mean age of the improved patients was lower than the patients who did not recover, but the difference was not statistically significant (P-value=0.058). In the pulmicort group of patients, there was a meaningful age difference between improved and not-improved patients (P-value=0.006).

Table 1: Statistical indicators regarding the age of the participants in the research

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>mean</th>
<th>median</th>
<th>mode</th>
<th>Standard deviation</th>
<th>minimum</th>
<th>maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmicort</td>
<td>52.5</td>
<td>53</td>
<td>57</td>
<td>6.11</td>
<td>39</td>
<td>61</td>
</tr>
<tr>
<td>systemic corticosteroid</td>
<td>50.47</td>
<td>50</td>
<td>42</td>
<td>6.77</td>
<td>40</td>
<td>61</td>
</tr>
</tbody>
</table>

Table 2: Results of regression analysis of the main hypothesis

<table>
<thead>
<tr>
<th>Predictive variable</th>
<th>regression coefficients B</th>
<th>Standard deviation error</th>
<th>Wald test*</th>
<th>Odds ratio</th>
<th>95% confidence interval of OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>1.90</td>
<td>0.63</td>
<td>8.99</td>
<td>6.68</td>
<td>1.93,23.12</td>
<td>0.003</td>
</tr>
<tr>
<td>Gender</td>
<td>2.44</td>
<td>0.66</td>
<td>13.46</td>
<td>11.48</td>
<td>3.13,42.28</td>
<td>0.000</td>
</tr>
<tr>
<td>age</td>
<td>-0.065</td>
<td>0.02</td>
<td>10.06</td>
<td>0.94</td>
<td>0.9,0.98</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Significant at the error level of 0.01

Table 3: The difference in the effectiveness of two drugs in patients with AOPA

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>systemic corticosteroid</th>
<th>pulmicort</th>
<th>Non-effective</th>
<th>Effective</th>
<th>Chi-square</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>17 (47.2%)</td>
<td>8 (22.2%)</td>
<td>51 (31.2%)</td>
<td>28 (77.8%)</td>
<td>4.96</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Table 4. The difference in the effectiveness of two drugs in patients with AOPA on the basis of gender

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Sex</th>
<th>Non-effective</th>
<th>Effective</th>
<th>Chi-square</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic corticosteroid</td>
<td>men</td>
<td>11 (68.8%)</td>
<td>5 (31.2%)</td>
<td>5.35*</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>women</td>
<td>6 (30%)</td>
<td>14 (70%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>17 (47.2%)</td>
<td>19 (52.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmicort</td>
<td>men</td>
<td>7 (46.7%)</td>
<td>8 (53.3%)</td>
<td>8.89*</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>women</td>
<td>1 (4.8%)</td>
<td>20 (95.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>8 (22.2%)</td>
<td>28 (77.8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Obtained from Fisher exact test
DISCUSSION

According to the results of this study, the number of recovered patients in the pulmicort group was strongly higher than these subjects in the systemic corticosteroid group. There have been a number of studies regarding the efficacy of budesonide for various kinds of obstructive pulmonary diseases. Meltzer et al.²² used budesonide at 160mg twice daily through a pressurized metered-dose inhaler (PMDI) to evaluate its efficacy vs placebo in pediatric patients with asthma and observed its considerable treatment effects. In the study conducted by Szafranski et al.,²⁶ budesonide/formoterol improved lung function and all symptoms of chronic obstructive pulmonary disease including breathlessness, chest tightness, cough and night-time awakenings and also reduced the severe exacerbations of the COPD. Tashkin et al.²⁶ administered budesonide/formoterol via PMDI in patients with frequent exacerbations of COPD and observed reductions in exacerbations of 20-25% for budesonide-containing treatments compared with formoterol and placebo. In the study of Calverley et al.,²³ budesonide reduced the number of oral corticosteroid courses given due to exacerbations of COPD compared with placebo. In a randomized controlled study carried out by Arulparithi et al.²⁴ the efficacy of nebulized budesonide with that of oral prednisone was compared in the treatment of children with acute severe asthma and significant improvement of Peak Expiratory Flow Rate levels was found in the study group who received budesonide versus control group. In the study by Szefler et al.²⁵ conducted on children with mild asthma over a period of 52 weeks, although both corticosteroids provided acceptable asthma control but the percentage of subjects who required oral corticosteroid over the study period was lower in budesonide group (25.5%) vs montelukast group (32%).

This study showed the higher chance of recovery in female patients compared with male patients in both treated groups of AOPA patients.
Aryal et al.\textsuperscript{26} showed that gender influences on COPD in its prevalence, comorbidities, and response to different ways of treatment. They expressed that in acute exacerbations and hospitalizations of COPD, the chance of survival in women is higher than men. Cao et al.\textsuperscript{27} assessed hospital admissions for acute exacerbations of COPD and found a higher rate of hospital admissions per year in men compared with women. In a pulmonary rehabilitation program, Haggerty et al.\textsuperscript{28} applied two health-related quality of life scales including Chronic Respiratory Disease Questionnaire the Pulmonary Function Status Scale and found that female participants of the study had a better status in terms of the mastery and emotion subscales of the first and the psychosocial subscale of the latter.

This study demonstrated the lower chance of recovery in AOPA patients with aging. This result is in consistent with the study conducted by Connolly et al.\textsuperscript{10} in which the rate of inpatient and 90-day mortality in very elderly patients with a COPD exacerbation was approximately three times higher than younger patients. With respect to this fact that population in Iran is aging, COPD will found more significance for the health care system in the future.

**CONCLUSION**

Pulmicort was shown to be an effective treatment for the patients with AOPA. The chance of recovery in patients who received pulmicort was higher than patients of systemic corticosteroid group. Moreover, the chance of recovery in both treatment groups in women was higher than men. There was an indirect relationship between the chance of recovery and age of patients. The difference in recovery between younger and older ages was statistically significant in the group of patients who received pulmicort. Overall, it can be concluded that pulmicort is more effective than systemic corticosteroid in the treatment of AOPA no matter what is gender.

**Limitations:** Awareness of the history of patients' lifestyles can be one of the factors for achieving more reliable results. We had no information regarding the patients' lifestyles to be able to analyze results based on various scores of life style. Furthermore, the lack of adequate and comprehensive studies in this regard is one of the limitations of this study.

**Agreement:** Zia Hejripour (Gather the data and editing the article), Saeed Shiralizadeh (Analysis the data and prepare the article), Gholamhosein Bagheri (Gather the data and prepare the article), Masoud Shahabian (Analysis and editing the article). AJA University of Medical Science contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. PM contributed in the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

**REFERENCES**


