Allergologia et immunopathologia
Sociedad Española de Inmunología Clínica, Alergología y Asma Pediátrica
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ORIGINAL ARTICLE

OPEN ACCESS

# Effect of combined glucocorticoid therapy on bronchial asthma dynamics

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Received 21 July 2021; Accepted 30 September 2021
Available online 1 January 2022

**KEYWORDS**
Bronchial Asthma;
Exacerbation;
Glucocorticosteroids;
Inhalation;
Peak Flow Rate;
Therapy

**Abstract**
This work is aimed to compare the effectiveness of parenteral and inhalation bronchial asthma treatment in combination with glucocorticosteroids and bronchodilators. The study was conducted in 2020 in Botkin City Clinical Hospital (Moscow, the Russian Federation). Case histories of 106 patients diagnosed with bronchial asthma exacerbation of moderate severity were analyzed. Patients were divided into two equal groups based on the therapy method: (1) Group 1 received systemic glucocorticosteroids parenterally in combination with inhalation glucocorticosteroids; (2) Group 2 received systemic glucocorticosteroids parenterally, but inhalation therapy was performed with a nebulizer. Clinical manifestations of bronchial asthma have been recorded. During hospital admission, the breath rate was 22.0 for Group 1 and 21.5 for Group 2, $P \geq 0.05$, and heart rates were 93.0 and 92.5, respectively ($P \geq 0.05$). All indices (blood saturation, breath rate, peak output rate) in Group 1 remained unchanged 4 h after the start of the therapy, while in Group 2, peak flow rate changed to 53.5% with a median increase of 72.0 ml over 4 h, $P \leq 0.05$. On Day 3, patients of Group 1 demonstrated a peak flow rate of 59.5%, $P \leq 0.05$, and on Day 10, patients of Group 2 had a peak output rate of 53.0 and 59.5%, respectively ($P \leq 0.05$). Systemic glucocorticoids were eliminated in 47 patients of Group 1 and in all patients of Group 2. The treatment tactics applied in Group 2 resulted in faster and more significant improvement in patients diagnosed with bronchial asthma exacerbation. Both treatment regimens showed high results.


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https://doi.org/10.15586/aei.v50i1.481

## Introduction

One of the most severe respiratory disorders nowadays is bronchial asthma.[1-4] The prevalence of this disease is constantly increasing in all countries worldwide.[2]

There are several ways to administer medications for bronchial asthma treatment[4]: orally, parenterally, or through inhalation.[5] The latter method is increasingly used in medicine because of the small number of systemic adverse reactions and the high local treatment effect.[6]

The peculiarity of bronchial asthma is that this condition affects all age groups. According to the World Health Organization, about 4–6% of the population worldwide suffer from chronic forms of bronchial asthma (https://www.who.int/ru/news-room/fact-sheets/detail/asthma). Bronchial asthma exacerbation symptoms include feelingof shortness of breath and coughing even with small physical exertion, as well as a feeling of chest tightness.[7] Generally, these symptoms can occur independently or in combination. The presence of bronchial asthma significantly aggravates the lives of these patients. The advancement in the treatment of bronchial asthma has not contributed to a reduction in the incidence of this condition in the population.[8]

Oxygen therapy,[9,10] glucocorticoids,[11] and bronchodilators[12] are the main medical means used to treat bronchial asthma.[13] Their combined application can significantly reduce the severity of bronchial asthma symptoms. For example, oxygen therapy aims to eliminate hypoxemia and reduce the risk of cardiovascular complications associated with high-dose beta-2 agonists.[14] Bronchodilators help alleviate bronchial spasms. The role of systemic glucocorticosteroids is wider and they involve in not only arresting bronchial spasm by accelerating it but also providing an anti-inflammatory effect.[15] Therefore, glucocorticosteroids should be prescribed as a mandatory treatment for all forms of bronchial asthma, except for the mild forms. Glucocorticoids are described below as a group of drugs, considering their pharmacodynamic properties.

Among natural glucocorticosteroids, cortisone and hydrocortisone are widely used in medical practice, along with synthetic and semisynthetic preparations based on them.[16-18] Glucocorticosteroid action is multifaceted, targeting several factors that cause inflammation in the body. Affected factors include cellular and vascular components of the inflammatory process, with the effect on mediators, through which lysosomal membrane stabilization occurs.[19] Due to the stabilization of membranes, the exit of proteolytic enzymes becomes more difficult, leading to a significant reduction in the processes of tissue destruction. Pronounced glucocorticosteroid effects include a reduction in capillary permeability, thus affecting the exudative stage of the inflammatory process.[20,21] At the immune system level, reduction of leukocytes accumulation in the edema area and activity of fibroblasts and macrophages are observed.[22]

In the case of pharmacodynamic therapy, the use of glucocorticosteroids is associated with their specific characteristics, which determine the prescription of a certain drug.[23,24] Specifically, in anesthesiology and intensive care medicine, glucocorticosteroids are prescribed for hypotension in cases of extensive bleeding or heart failure, for shock caused by trauma or infectious processes, for acute allergic reactions such as Quincke's edema, and in case of anaphylactic shock.[25] Although glucocorticosteroids are always used in shock conditions, their effectiveness is not fully understood because shock involves many different causal factors, and considering all of them is impossible. In allergic reactions, the prescription of glucocorticosteroids is not always warranted as they have a delayed effect. For example, for hydrocortisone, the main effect is observed after 3–8 h, and in some severe cases, the injection of adrenaline is more justified to avoid bronchial spasm.[26]

For long-term treatment, prescription of glucocorticosteroids is based on specific features. Factors such as administration duration and dosage of glucocorticosteroids are associated with the risk of adverse reactions.[27] The risks are at their greatest after 2 weeks of applying maximum doses.[16] Major adverse reactions to high-dose glucocorticosteroids are associated with the impaired or suppressed adrenal function.[8] Adverse events include insomnia, emotional lability, increased appetite, pancreatitis, atherosclerosis, glaucoma, and osteoporosis. Risk factors include high blood pressure and high blood sugar levels, diabetes mellitus, and gastroduodenal ulcer.[7] Therefore, glucocorticosteroids administration in high doses and over an extended period should be treated with care, given the adverse effects. Moreover, long-acting glucocorticosteroids are known to prevent respiratory distress, leading to a 40–50% reduction in mortality and complications in premature infants.[7]

If glucocorticosteroids are prescribed in low doses, there are no adverse effects, while prescription of high doses and their prolonged use (more than 10 days) lead to the development of adrenal insufficiency. Therefore, it is necessary to gradually reduce the dosage of drugs taken. In this case, for the complete restoration of the adrenal glands functioning, a course of therapy should last from 2 months to a year and a half.[6]

The effect of glucocorticoids in combination therapy with other drugs, for bronchial asthma, has not been elucidated completely. Most studies available on bronchial asthma therapy do not search for its most optimal options that involve the use of glucocorticosteroids, which determined the relevance of the present research.[1,3] The novelty of this work lies in the comparative analysis of the effectiveness of parenteral and inhalation method of glucocorticosteroid administration as part of combined therapy based on the authors' observations of 108 patients. The authors suggest that the inhalation method of glucocorticosteroid administration shall be more effective compared to the conventional parenteral method in combined bronchial asthma therapy.

The purpose of the study was to perform a comparative analysis of parenteral and inhalation methods efficacy in combined treatment of bronchial asthma. The objectives of the study were: (1) to establish the efficacy indicators (duration of therapy, obstruction, dyspnea) for each therapy; (2) to identify and propose an optimal algorithm for the management of patients with bronchial asthma.

## Material and methods

### Materials

The study was carried out from January to December 2020 at Botkin Moscow City Clinical Hospital, Russian Federation. Medical history cases of 106 patients hospitalized during this period were analyzed. The mean age of the patients was 54.3 ± 3.2 years. In terms of gender differences, the study enrolled 80 females (average age of 51.4 ± 2.7 years) and 26 males (average age of 54.7 ± 3.9 years). There were no significant differences between female and male patients by age. All participants were divided into two groups, Group 1 (53 patients, 40 females and 13 males) and Group 2 (the same number of patients), according to the treatment tactics. A random sampling methodology was used to assign patients to groups.

### Study design

A voluntary written and informed consent was obtained from every patient who participated in this study, and the Participant Information Sheet was signed. The research was conducted according to generally accepted ethical and moral norms and principles in medical practice. The study design was approved in the Ethics Committee meeting conducted at Botkin Moscow City Clinical Hospital (Protocol No. 32-099). Also, the work described has been carried out in accordance with Declaration of Helsinki. For possible participation in the study, a detailed review of the patients' medical history was carried out by allergy and phlebology specialists. Patients who volunteered informed consent to participate and had no chronic diseases that could cause adverse events while taking glucocorticosteroids were included in the study. All patients had moderate bronchial asthma exacerbation. Patients diagnosed with gastric ulcer, pancreatitis, atherosclerosis, glaucoma, osteoporosis, high blood pressure, hyperglycemia, or diabetes mellitus were not included.

### Research methods

Group 1 was treated with systemic glucocorticosteroids parenterally (prednisolone solution, 120 mg dose). Besides, patients received an inhalation therapy with glucocorticosteroids at a dose of 1000 mcg daily (mcg; beclomethasone in the form of propionate, Clenil Jet, manufactured by Chiesi Farmaceutici S.p.A.). Group 2 also received parenteral systemic glucocorticosteroids at the same dose but as an inhalation treatment with nebulizer (Benacort, 0.5 ml/ml, the standard dose was 3 ml, manufactured by Pulmomed).

Syndromes of bronchial asthma were treated with Berodual (ipratropium bromide, 0.26 mg and fenoterol hydrobromide, 0.5 mg). Using a nebulizer, the medicine was taken every 3 h for 1 h, after 60 min, and finally every 4 h. Some patients have taken medications to expel excess sputum in case of secretion accumulation. Moreover, antibacterial treatment and oxygen therapy have been provided in certain cases.

All patients underwent electrocardiography, a general clinical blood analysis, pulse oximetry, and peak flow measurement procedures. Furthermore, patients who consented to the study were given a questionnaire.

### Statistical analysis

The data obtained were entered into Excel 2016 (Microsoft Inc., 2016, USA). Statistica v.7.0 software (StatSoft Inc., USA) was used for the statistical processing of the data matrix. The dataset was tested to match the distribution to the normal using the Shapiro–Wilk criterion. Nonparametric methods of statistical analysis were applied in the case of not normal distribution. The Mann–Whitney criteria were used for statistical analysis: the median and the 25 and 75% quartiles are provided in the text. Qualitative data were analyzed in percentage, which represen distribution of absolute and relative frequencies signs, with a minimum significance level $P \leq 0.05$.

## Results

There were no significant differences between Group 1 and Group 2 patients in terms of clinical signs of bronchial asthma during admission (Table 1). The daytime asthma attack frequency was 4.0 (median values of 25 and 75% from 3.0 to 7.0) for Group 1 and 5.0 (from 4.0 to 7.0) for Group 2. No significant differences between groups were noted for night attacks in their frequency of occurrence, amounting to 2.0 (1.5–3.0) and 2.0 (2.5–3.5), respectively, $P \geq 0.05$. For the number of beta-2 agonist doses, indices in both groups did not differ significantly as well. The requirement was 8.0 (6.0–9.0) for Group 1 and 7.5 (6.0–9.5) for Group 2, $P \geq 0.05$. Patients from both groups were found to have dyspnea on admission to the hospital. Thus, it was 22.0 (20.0–24.0) for Group 1 and 21.5 (19.5–23.5) for Group 2, $P \geq 0.05$. Dyspnea index values are displayed in breath rate.

Due to high heart rate values, patients from Groups 1 and 2 had tachycardia of moderate severity. The heart rates were 93.0 (83.5–98.0) and 92.5 (83.0–97.0) for Group 1 and 2, respectively, that is, $P \geq 0.05$. Pulse oximetry revealed the following blood saturation values: 91.0% (91.0–93.0%) and 92.0% (90.5–93.0%) for Groups 1 and 2, respectively, that is, $P \geq 0.05$. In addition, patients in both groups exhibited lower peak flow rate, amounting to 50.3% for Group 1

**Table 1** Pretreatment indicators.

| Indicator | Group 1 | Group 2 |
|---|---|---|
| Frequency of asthma attacks | | |
| - During daytime | 4.0 | 5.0 |
| - At night | 2.0 | 2.0 |
| Number of beta-2 agonist doses | 8.0 | 7.5 |
| Shortness of breath in respiratory rate | 22.0 | 21.5 |
| Heart rate | 93.0 | 92.5 |
| Blood saturation | 91.0% | 92.0% |
| Peak flow rate decrease | 50.3% | 45.0% |

**Table 2** Indicators after the start of therapy, Day 1.

| Indicator | Group 1 | Group 2 |
|---|---|---|
| Shortness of breath in respiratory rate | 19.5 | 20.0 |
| Blood saturation | 95.5% | 96.0% |
| Peak flow rate increase in 1 h after the start of therapy | Per 41.0 ml | Per 70.0 ml |

(35.0–75.0%) and 45.0% for Group 2 (30.0–67.0%). These values of maximum peak flow rate were assigned to the red zone, which indicates an increased airway obstruction.

After 1 h of therapy (Table 2), positive changes in dyspnea indices were noted. Namely, it decreased to 19.5 (from 18.0 to 20.0) per 1 min for Group 1 and 20.0 (from 18.5 to 20.5) for Group 2 ($P \geq 0.05$). High blood oxygen saturation rates were also registered, comprising 95.5% in Group 1 and 96.0% in Group 2 (in both cases, $P \leq 0.05$ when compared to the pretherapy values). Already 1 h after start of the therapy, the peak flow rate increased by 41.0 ml (from 6.0 to 82.0) for Group 1 and by 70.0 ml (from 40.0 to 112.0) for Group 2, $P \leq 0.05$ between the groups. Four hours after the beginning of treatment, blood saturation, breath rate, and the peak flow rate did not change significantly in Group 1. For Group 2, the peak flow rate changed up to 53.5% (from 44.0 to 61.0%) 20 min after the start of the therapy. Moreover, the increase in median peak rate was 72.0 ml (from 52.0 to 127.0) in 4 h, $P \leq 0.05$.

Consequently, both treatment methods proved to be effective and significantly improved the condition of patients within 4 h of admission to the hospital. At the same time, the therapeutic regimen offered to Group 2 patients showed slightly better results, as higher peak flow rate values were obtained.

The second day of treatment demonstrated significant improvements (Table 3). Thus, the frequency of asthmatic choking attacks reduced significantly to 2.5 (1.5–3.5) and 3.0 (2.0–4.0) in Groups 1 and 2, respectively, $P \leq 0.001$ (Figure 1).

The beta-2 agonist requirement indices of patients were only 2.5 (1.0–3.5) and 2.0 (1.5–3.0) in Groups 1 and 2, respectively, $P \leq 0.001$ (Figure 2). Besides, dyspnea indices also decreased to 18.0 in Group 1 (17.0–19.5) and 18.5 in Group 2 (17.5–19.0), $P \leq 0.05$. Blood oxygen saturation parameters increased to 95.5% (94.5–96.5%) in Group 1 and 96.0% in Group 2 (95.0–97.0%), (Figure 3, $P \leq 0.05$). On the other hand, no statistically significant differences were observed between the two groups.

**Table 3** Indicators on Day 2 of therapy.

| Indicator | Group 1 | Group 2 |
|---|---|---|
| Frequency of asthma attacks | 2.5 | 3.0 |
| Patients' requirement for beta-2 agonists | 2.5 | 2.0 |
| Shortness of breath in respiratory rate | 18.0 | 18.5 |
| Blood saturation | 95.5% | 96.0% |

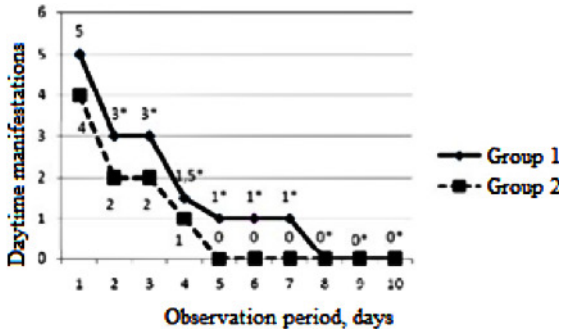


**Figure 1** Number of daytime manifestations of bronchial asthma in patients of both study groups.
Note: *Differences are significant at $P \leq 0.05$.

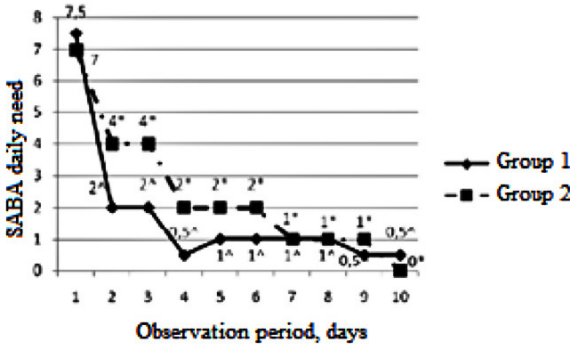


**Figure 2** Indicators of patient's demand for sympathomimetics in both subgroups.
Note: *$P \leq 0.05$ for Group 1, ^$P \leq 0.05$ for Group 2 (according to the Mann-Whitney U-test results); **SABA: short-acting beta-2 agonists

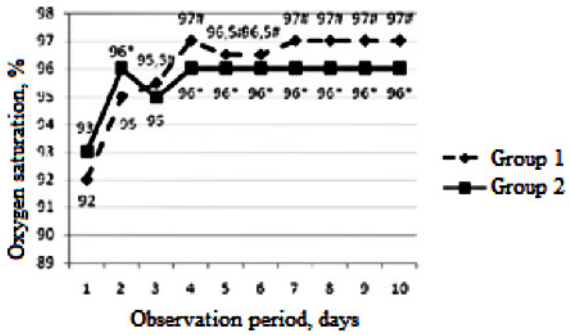


**Figure 3** Changes in oxygen saturation indices in patients of both subgroups.
Note: Differences are significant for Group 1 ($P \leq 0.05$) and *for Group 2 (according to the Mann-Whitney U-test results).

On the third day of treatment (Table 4), the status of Group 1 patients improved significantly. Thus, the peak flow rate was 59.5% (from 45.0 to 70.0), $P \leq 0.05$. Further, up to the tenth day of therapy, the indicators did not change significantly, and the peak flow rate was 59.0% (from 45.5 to 63.0) (Figure 4).

For Group 2, these rates were 53.0% (42.0–62.0) on Day 3 and 59.5% (51.0–63.5) on Day 10, $P \leq 0.05$, when compared with Group 1. On analysing the periods preceding the admission and after the start of treatment, these

**Table 4** Indicators on Days 3–10 of the therapy.

| Indicator | Group 1 | Group 2 |
|---|---|---|
| Peak flow rate | 59.0–59.5% | 53.0–59.5% |
| Withdrawal of systemic glucocorticosteroids | 47 patients out of 53 | All 53 patients |

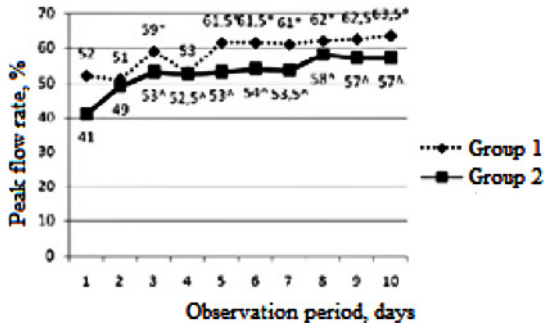


**Figure 4** Parameters of peak flow rate in the morning in the two groups studied.
Note: *P ≤ 0.05 for Group 1, ^P ≤ 0.05 for Group 2 (according to the Mann–Whitney U-test results).

indicators moved from the red zone to the yellow–green zone. Systemic glucocorticosteroids were withdrawn in 47 out of 53 patients in Group 1 and all 53 patients in Group 2.

Hence, glucocorticosteroid therapy showed high outcomes for bronchial asthma treatment in both groups, regardless of the parenteral or inhalation administration method. Within 10 days of therapy, the overall condition of the patients improved considerably, and the disease symptoms were successfully eliminated.

The obtained results state that both algorithms for treating patients with bronchial asthma are effective:

1. systemic glucocorticosteroids administered parenterally (solution of prednisolone, a dose of 120 mg) – inhaled glucocorticosteroids, a dose of 1000 mcg (beclomethasone in dipropionate form), daily.
2. systemic glucocorticosteroids administered parenterally (solution of prednisolone, a dose of 120 mg) – using nebulizer (Benacort, 0.5 ml/ml, standard dose of 3 ml) every 1–3 h for 1 h, then every hour, and finally every 4 h.

However, according to the observations, the condition of patients improves faster when using the inhalation method. As such, it can be recommended as a more effective one. This conclusion confirms the assumption stated in the introduction. Although both methods are quite effective in treatment of bronchial asthma, inhalation therapy was shown to facilitate the recovery.

## Discussion

In bronchial asthma treatment by glucocorticosteroids, the therapeutic approach plays a key role.[28] This is due to the frequency of adverse events, because the prescribed oral doses of glucocorticosteroids[29] are significantly higher when prescribed with inhalation.[30] Due to the difference in dosage, the effect of glucocorticosteroids through inhalation was mostly local because only the ingested pulmonary fraction dose enters the bloodstream, which is much lower compared to amounts entering the bloodstream after oral administration.[31] And yet, when glucocorticosteroids are inhaled for a long time (from 4 days), breathing function improves and (in some cases) normalizes, the amplitude of peak flow rate fluctuations during the day decreases, and the need for patients to take systemic glucocorticosteroids reduces.[32] This was also demonstrated in this study. Thus, by the tenth day of therapy, almost all patients in both groups did not require systemic glucocorticosteroids. Moreover, long-term administration of glucocorticosteroids through inhalation reduces the likelihood of bronchospasm, as well as irreversible airways obstruction.[33] Other data suggest that the frequency of calls for emergency medical care,[34] mortality, and the frequency of bronchial asthma exacerbations decreased significantly.[35]

Scientists have noted that even with severe exacerbations, glucocorticosteroids prescribed in the early stages of the disease can be effective without the need to hospitalize the patient.[36] Therefore, when a patient's condition is assessed as very serious, systemic glucocorticosteroids are the first medications prescribed.[37] Usage of these drugs leads to rapid improvement of bronchial obstruction and reduces the likelihood of complications that may arise after the patient is discharged from the hospital. Nevertheless, the effectiveness of these drugs is questionable because their action is rather slow, and the likelihood of developing adverse events is quite high.[5,38] According to the British Thoracic Society, taking 1000 mcg of inhaled glucocorticosteroids is equivalent to taking 30–50 mg of prednisolone orally, although high doses of inhaled glucocorticosteroids are less dangerous than intake of systemic glucocorticosteroids.[38] For example, a study examining the efficacy of the Klenil drug found that its administration via nebulizer at a dose of 3200 mcg per day was most effective for bronchial asthma compared to a 1600 mcg dose. At the same time, the effect of the drug on the adrenal–pituitary system was no more negative than for placebo.[39,40]

Glucocorticoids have come a long way in a wide range of forms of administration, from systemic to inhalation. Inhalers come in many forms, but their aim is the same; they are designed to administer the drug. Furthermore, the optimal combination of the inhaler and the active ingredient itself can be selected. This study demonstrated that the use of the inhalation method has led to a more significant improvement in the condition of patients with asthma attacks. This is evidenced by the indicators of peak flow rate in patients already on the third day of therapy. Parenteral method is also quite effective (as evidenced by the improvement of indicators such as shortness of breath and blood saturation), but its effects are manifested later (on Day 10). Such conclusion expands contemporary idea about therapy based on glucocorticosteroids and bronchodilators as many works[3-5] are devoted to studying these methods and confirming their effectiveness. However, there is a lack of studies that give a comparative characteristic of these methods, as was done in this article when analyzing parenteral and inhalation methods. Similar

efforts were made in research by Wu et al.,[41] comparing intravenous and oral methods of glucocorticosteroids administration.

## Conclusions

It was found that the best therapeutic effect was achieved by treatment with a combination of inhaled and systemic glucocorticosteroids together with bronchodilators. Already on the third day of therapy, significant improvement of peak flow rate indices was registered in patients from Group 1 (59.5%, $P \leq 0.05$), with no significant changes up to the tenth day (59.0%). In Group 2, the peak flow rates were 53.0% on Day 3 and 59.5% on Day 10, $P \leq 0.05$, when compared with Group 1.

Systemic glucocorticosteroids were discontinued in 47 out of 53 patients in Group 1 and all patients in Group 2. The treatment regimen used in Group 2 for patients with moderately severe bronchial asthma made it possible to almost completely arrest the symptoms of the disease (dyspnea, increased heart rate [tachycardia]). Such results were achieved in a shorter time compared to Group 1. This therapy regimen can also reduce the financial costs of patients' hospitalization and therapy because the improvement of their condition is achieved within a shorter time and the probability of recurrent attacks after discharge from the hospital is drastically lower.

This study compares two methods of using glucocorticosteroids during bronchial asthma therapy. Their effectiveness is confirmed by the study results, but the systemic effect of glucocorticosteroids on the human body remains undisclosed. Thus, future research efforts may be aimed at finding alternative solutions for effective and rapid treatment of bronchial asthma without glucocorticosteroids. Colleagues can use the results of this study to select rational treatment regimens, while researchers may find it useful in achieving optimal treatment outcomes for patients.

## Conflict of interests

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

## Acknowledgments

Not applicable.

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