Assessment of Clinical Efficacy of Dexamethasone in Patients with Moderate COVID-19

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Анализ клинической эффективности дексаметазона у пациентов со среднетяжелым течением COVID-19

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Summary

The host immune response, primarily manifested by hypercytokinemia, obviously plays a key role in the development of severe novel coronavirus disease, COVID-19. Currently, numerous therapies aimed at suppressing the hyperinflammatory response and the «cytokine storm» are being investigated. One of these methods is the use of corticosteroids, particularly dexamethasone.

The aim was to assess the clinical efficacy of dexamethasone in patients with moderate bilateral multifocal pneumonia caused by SARS-CoV-2 virus.

Material and methods. Sixty-nine patients aged from 31 to 88 years hospitalized in Almazov National Research Center and the Semashko City Hospital No 38 with SARS-CoV-2 coronavirus infection complicated by moderate (semiquantitative visual pulmonary lesion grading system CT 2–3 corresponding to 25–50% and 50–75% parenchymal involvement, respectively) community-acquired bilateral multifocal pneumonia were retrospectively studied. Group 1 included 39 patients with moderate coronavirus infection who received therapy according to the current version of the temporary guidelines (TG) of the Ministry of Health of the Russian Federation, including dexamethasone. The drug was administered parenterally twice daily in a dosage of 12 mg in the morning and 8 mg in the evening for the first three days, then the dose was gradually reduced over 5–7 days. No Interleukin-6 inhibitors were administered to patients in this group. Group 2 was composed of 30 patients who received therapy according to the current version of TG, including a parenteral interleukin-6 inhibitor (tocilizumab, olokizumab, or sarilumab) following the standard regimen. Patients in this group were not administered with dexamethasone.

Results. CT scans corresponding to severity grade 3 and 4 (50–75% and >75% involvement, respectively) lung lesions on Day 7 were found in 35.89% of group 1 patients, while similar CT scans were found in 50% of patients who received interleukin-6 inhibitors (P=0.33). On Day 14 no significant differences in this parameter were revealed as well. Duration of fever in the dexamethasone group was 3.69 (0.62; 6.76) days, while in the control group it was 3.95 (0.61; 7.29) days (P=0.98). There was a tendency to decreased blood C-reactive protein (CRP) values in the dexamethasone group on days 5 and 7. The frequency of transfer of patients to the ICU and hospital stay duration did not differ significantly between the groups.

Conclusion. Dexamethasone has comparable clinical efficacy with IL-6 antagonists in the comprehensive treatment of patients with moderate COVID-19 disease, which is confirmed by the chest CT evolution, duration of fever, and changes in serum CRP.

Keywords: COVID-19; glucocorticoids; interleukin-6 inhibitors

Conflict of interest. The authors declare no conflict of interest

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Introduction

In 2019, the SARS-CoV2 virus, which causes the novel coronavirus infection, was detected for the first time in Wuhan, Hubei province, China [1]. In a short period of time, the outbreak of this disease reached pandemic proportions. According to statistics, as of March 12, 2021, 119,748,246 cases had been identified worldwide. Russia ranks fourth among all countries in the number of cases (4,341,381) [2, 3].

Coronavirus infection remains a major challenge for scientists and clinicians worldwide. The clinical picture of COVID-19 has a wide range of manifestations, from asymptomatic and mildly symptomatic disease to severe pneumonia with extensive lung involvement and hyperinflammatory syndrome [4, 5].

Some authors identify three degrees of severity of coronavirus infection: mild (with nonspecific symptoms such as malaise, dry cough, fever), moderate (viral pneumonia with cough, fever and, possibly, hypoxia), and severe (extrapulmonary systemic hyperinflammatory syndrome). Obviously, the main role in severe COVID-19 is played by the host immune response, which primarily manifests as hypercytokinemia [6, 7].

Numerous treatment approaches aimed at suppressing the hyperinflammatory response are being studied, but none of them has convincing evidence of efficacy. The use of corticosteroids, particularly dexamethasone, is one of these treatment modalities. Currently, many studies evaluating the efficacy and safety of dexamethasone for patients with moderate to severe coronavirus infection have been conducted [8, 9].

In March 2020, Jamaati H. et al. studied 50 patients, 25 of whom received dexamethasone 20 mg for the first five days of hospitalization and then 10 mg during days six through ten. According to the results of this study, 92% of patients in the dexamethasone group and 96% in the control group (P=0.500) required noninvasive ventilation, while 44% in the dexamethasone group and 52% in the control needed mechanical lung ventilation. The study authors pointed out that improvement on CT scans was seen in 40% of patients in the dexamethasone group vs 12% of patients in the control group [10].

A controlled, open-label, randomized trial RECOVERY found a reduction in 28-day mortality among patients who required oxygen therapy or ventilator support and were prescribed dexamethasone for ten days. There was also a reduction in 28-day mortality when dexamethasone was used seven days after the onset of disease. Among patients who received oxygen therapy, dexamethasone use was associated with a lower risk of being switched to invasive ventilation, and in those who were already on invasive ventilation it was related to a higher chance of successful weaning from mechanical ventilation [12].

However, according to a meta-analysis (March 2020), the use of corticosteroids can reduce viral clearance and increase length of stay [7]. In December 2020, the results of another meta-analysis [9] were published, which included randomized clinical trials and observational cohort studies evaluating the effect of corticosteroids in COVID-19. The authors reported that the effect of dexamethasone on viral clearance and the development of secondary infections could not be reliably assessed due to insufficient data. In contrast, they confirmed a significant reduction in 28-day mortality when using corticosteroids, particularly dexamethasone, in COVID-19. Several medical societies have decided to include dexamethasone in the treatment protocol for patients with COVID-19 [11].

In summary, corticosteroids, on the one hand, can indeed suppress the hyperimmune response and, on the other hand, increase the risk of opportunistic or nosocomial infections, inhibit the hypothalamic-pituitary-adrenal axis, induce hyperglycaemia in predisposed persons or in patients with diabetes mellitus, and reduce viral clearance [8, 13].

Due to contradictory data on usefulness of steroids in COVID-19, we conducted a retrospective study to evaluate the effectiveness of dexamethasone in patients with moderate bilateral multifocal viral pneumonia caused by SARS-CoV-2.

Aim — to determine the clinical efficacy of dexamethasone in patients with moderate bilateral multifocal viral pneumonia caused by SARS-CoV-2 virus.

Material and Methods

A cohort retrospective clinical study was performed in 69 patients aged 31 to 88 years (mean age 60 years) with coronavirus infection caused by SARS-CoV-2, complicated by moderate community-acquired bilateral multifocal viral pneumonia and admitted to Almazov Scientific Research Center and the Semashko City Hospital No.38, Saint Petersburg. All patients were admitted to the intensive care wards of infectious diseases departments and required low-flow oxygen therapy through nasal catheters or a mask due to clinical manifestations of respiratory failure.

Inclusion criteria were patient's age 18 to 90 years, moderate clinical manifestations of COVID-19 (fever above 38.0 °C, respiratory rate >22 /min, dyspnea on exercise, SpO_2 <95%, serum C-reactive protein (CRP) level >10 mg/l, abnormal chest CT or X-ray characteristic of viral damage (moderate

severity, corresponding to CT grade 2–3 according to the semi-quantitative visual assessment scale).

Exclusion criteria were autoimmune disease, cancer, routine glucocorticoid therapy, history of chemotherapy, and chronic kidney disease (CKD).

Group 1 included 39 patients with moderate coronavirus infection who received therapy according to the Temporary Guidelines (TG) on prevention, diagnosis and treatment of novel coronavirus infection (COVID-19) of the Ministry of Health of the Russian Federation, Version 8.1 (01.10.2020), including dexamethasone. Dexamethasone was administered on the following indications: combination of CT findings (progression of lesion volume over 3–5 days with two or more of the following: decreased SpO_2 <93% on ambient air, CRP level >40 mg/l; fever >38°C for 5 days). Dexamethasone treatment was started, on average, on day 10 from the onset of the disease. The drug was administered parenterally twice daily in a dosage of 12 mg in the morning and 8 mg in the evening during the first three days, then the dose was tapered over 5–7 days. Interleukin-6 inhibitors were not used in patients of this group.

Group 2 was composed of 30 patients who received therapy according to the current version of TG of the Russian Ministry of Health, including parenteral interleukin-6 inhibitors (tolicizumab, olokizumab, sarilumab) in standard regimens. Indications for prescription of interleukin-6 inhibitors according to TG were progression of interstitial lung damage on chest CT scan in combination with two and more of the following: progressive decrease in SpO_2; CRP>60 mg/l or an increase in CRP 3 or more times its value on admission; fever >38°C for 5 days; WBC count $<3.0\times10^9$/l; absolute lymphocyte count $<1\times10^9$/l; blood ferritin level >500 ng/ml; plasma IL-6 level >40 pg/ml. Patients of this group did not receive dexamethasone or other glucocorticoids.

The following criteria were used to evaluate the efficacy of treatment: chest CT scan on days 1, 7, and 14 from admission, presence/absence of body temperature elevation (>37.2°C), C-reactive protein, ferritin, WBC and lymphocyte counts on days 1, 2, 3, 5, 7, and 10.

Comparative analysis of quantitative variables was performed using Mann–Whitney test; qualitative variables were analyzed using Fisher's exact test. For quantitative variables the results were presented as *Me* (*Q1; Q3*) (median and interquartile range). For all statistical calculations, the level of significance was set to $P<0.05$.

Results

There were no significant differences between the groups in terms of gender, age, respiratory rate, use of noninvasive respiratory therapies, and comorbidities at baseline (Table 1).

According to data presented in Table 2, on day 7 CT findings corresponding to 3–4 degree of lung involvement were revealed in 35.89% of patients from group 1, while similar CT patterns were found in 50% of patients receiving interleukin-6 inhibitors ($P=0.33$). On day 14 there were also no significant differences in this parameter. Duration of body temperature elevation in dexamethasone group was 3.69 (0.62;6.76) days, and 3.95 (0.61;7.29) days in the control group ($P=0.98$). There were no statistically significant differences between the groups in changes in peripheral blood lymphocyte count and serum C-reactive protein level during the first 10 days after enrollment. The trend toward lower CRP values on days 5 and 7 in the dexamethasone group is worth noting. The rate of transfers to ICU and length of hospital stay also did not differ significantly.

Discussion

Glucocorticoids have previously been used for coronavirus-associated syndromes, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). However, the evidence base for their efficacy in these infections was rather limited (level of evidence 3) due to the lack of randomized controlled trials [13–15, 17].

The RECOVERY study was designed to perform a rapid and reliable assessment of the effect

Table 1. Comparative characteristics of groups by sex, age and comorbidities.

Parameters	Values in groups		*P*
	Group 1, *n*=39	Group 2, *n*=30	
Age	60.02 (56.24; 63.8)	61.20 (55.54; 72.53)	0.87
Sex	24 female/15 male	17 female/13 male	0.81
Respiratory rate more than 22 per minute on admission	39	30	1.00
Oxygen therapy through a face mask with a flow rate up to 15 l/min	39	29	1.00
Non-invasive mechanical lung ventilation	0	1	1.00
Comorbidities			
Diabetes mellitus	9 (23.07%)	3 (10%)	0.21
Obesity	7 (17.94%)	6 (20%)	1.000
Hypertension	25 (64.01%)	13 (43.33%)	0.095
Coronary heart disease	11 (28.21%)	4 (13.33%)	0.16
History of cancer	0	1 (3.33%)	0.44

Table 2. Comparative characteristics of groups by main parameters of clinical outcome and laboratory markers.

Parameter	Values in groups		*P*
	Group 1, *n*=39	Group 2, *n*=30	
CT grade 3–4, day 7	14 (35.89%)	15 (50%)	0.33
CT grade 3–4, day 14	4 (10.25%)	3 (10%)	1.00
Fever duration, days	3,69 (0,62; 6,76)	3,95 (0,61; 7,29)	0.98
C-reactive protein, mg/l			
Day 1	29.26 (22.3; 36.25)	59.32 (32.99; 85.65)	0.14
Day 3	28.02 (10.76; 45.28)	49.96 (39.35; 66.12)	0.15
Day 5	28.32 (15.04; 41.61)	57.38 (40.43; 74.33)	0.14
Day 7	17.41 (11.67; 23.15)	24.36 (20.59; 28.13)	0.1
Day 10	22.98 (4.1; 41.86)	18.22 (9.49; 26.95)	0.17
Blood lymphocytes, absolute count per mm^3			
Day 1	1542 (1360; 1724)	1180 (994; 1366)	0.02
Day 5	1080 (760; 1400)	1350 (1135; 1565)	0,09
Day 7	1757 (1450; 2064)	1460 (742; 2178)	0,15
Day 10	1897 (1290; 2504)	1280 (777; 1783)	0,07
Transfer to ICU, patients	0	1	1.00
Adverse clinical outcome, patients	0	1	1.00
Length of hospital stay, days	15.17 (12.82; 17.52)	12.0 (8.18;15.82)	0.08

of available COVID-19 treatments on the 28-day mortality rate. This parameter is an essential though not the only indicator of treatment efficacy. In a randomized clinical trial involving 299 adults with moderate to severe COVID-19-induced ARDS, dexamethasone significantly (RR, 0.84; 95% CI, 0.54–1.32) increased the number of ventilator-free days in the ICU during the first 28 days of illness [12].

However, some researchers have raised concerns that high doses of corticosteroids (equivalent to 30 mg of dexamethasone per day) for viral pneumonia may be associated with adverse outcomes [18].

An open randomized multicenter trial conducted in Spain involving 277 patients with ARDS unrelated to COVID-19 showed a 15% reduction in 60-day mortality (from 36% to 21%) in patients treated with dexamethasone [20].

A recent meta-analysis including data from seven studies of glucocorticoid use in COVID-19 patients in critical care, including RECOVERY, showed that among patients receiving oxygen, dexamethasone use was associated with a lower risk of invasive ventilation or, for those already on invasive ventilation support, with a higher chance of successful weaning. Moreover, dexamethasone use increased the likelihood of a favorable outcome (RR 0.64; 95% CI, 0.50–0.82; $P<0.001$) and discharge from hospital within 28 days [19].

Nevertheless, it is important to note the heterogeneity of the groups compared in different RCTs and meta-analyses, all in terms of disease severity, doses and regimens of glucocorticoid administration. Slower clearance of viral RNA was observed in patients with SARS, MERS and influenza treated with systemic glucocorticoids, but the clinical significance of this fact is unknown [21]. In contrast to SARS, in which viral replication peaks in the second week of illness [22], viral shedding in SARS-CoV-2 appears to be significantly higher in the early stages and declines sharply on week 2–3 [23].

Our data demonstrated clinical efficacy of dexamethasone comparable to IL-6 antagonists in a group of patients with moderate COVID-19. The effect of dexamethasone on the 28-day mortality in patients with COVID-19 on respiratory support suggests that immunopathological processes may predominate as early as during the second week of disease, with active viral replication playing a secondary role. This hypothesis cautions against extrapolating the clinical effect of dexamethasone in patients with COVID-19 to those with other viral respiratory diseases [16, 24, 25].

Certain limitations and drawbacks of the study should be noted. The patient assessment using severity scales, such as SOFA, SAPS or APACHE-II, was not used, since only patients with moderate COVID-19 were included in the retrospective analysis. Obviously, a patient with respiratory failure is affected by a variety of disease-modifying factors such as antiviral and antibacterial therapies, anticoagulant regimens, sedation and analgesia, respiratory support techniques, infectious complications, and others. Since it is often extremely difficult to discern the influence of a particular factor in real practice, we have assumed an equal impact of these factors on the patients in the studied groups. Also, it is necessary to bear in mind that only a single-factor analysis was performed. Thus, further research in this area through conducting a prospective randomized controlled trial is necessary to confirm the results obtained.

Conclusion

Dexamethasone has comparable clinical efficacy to IL-6 antagonists in the comprehensive treatment of patients with moderate COVID-19, as confirmed by the changes in chest CT scan, duration of elevated body temperature, as well as the trends in serum CRP level.

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