STUDY OF THE EFFECTIVENESS OF METHYLPREDNISOLONE AT DIFFERENT STAGES OF INPATIENT CARE FOR PATIENTS WITH PNEUMONIA CAUSED BY A NEW COVID-19 CORONAVIRUS INFECTION

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Glucocorticoid therapy for a cytokine storm is one of the mainstays of managing the novel coronavirus disease COVID-19. The aim of this study was to evaluate the efficacy of methylprednisolone at different stages of medical care: in an intensive care unit (ICU) vs. a medical ward setting. Methylprednisolone therapy was delivered to 54 patients, amounting to 9% of the total patients hospitalized to the Federal Center of Brain Research and Neurotechnology of FMBA, Russia. Twenty-eight patients received methylprednisolone in the ICU setting; 26 patients, in a medical ward setting. The control group comprised 14 patients. Methylprednisolone was administered continuously, intravenously at 250 mg per day over the course of 3 days; the total dose was 750 mg. The analysis revealed a significant reduction in mortality in the group receiving methylprednisolone in a medical ward setting (7.7%) in comparison with the group receiving the drug in ICU (67.9%) and the control group (42.9%, $p < 0.001$). The need for mechanical ventilation was lower in the group receiving methylprednisolone in a medical ward (2 (7.7%), 20 (71.4%) and 7 (50%) cases, respectively, $p < 0.001$). Thus, preventive anti-inflammatory methylprednisolone therapy for delivered in a medical ward setting reduces hospital mortality and the need for MV in patients with COVID-19-induced pneumonia.

Keywords: coronavirus infection, COVID-19, corticosteroids, viral pneumonia

ИССЛЕДОВАНИЕ ЭФФЕКТИВНОСТИ МЕТИЛПРЕДНИЗОЛОНА НА РАЗНЫХ ЭТАПАХ ОКАЗАНИЯ СТАЦИОНАРНОЙ МЕДИЦИНСКОЙ ПОМОЩИ ПАЦИЕНТАМ С ПНЕВМОНИЕЙ, ВЫЗВАННОЙ НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИЕЙ COVID-19

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Одним из основных направлений терапии пневмонии, вызванной новой коронавирусной инфекцией COVID-19, является применение средств, направленных на борьбу с цитокиновым штормом, в том числе глюкокортикостероидов. Целью настоящего исследования явилось изучение эффективности применения метилпреднизолона на разных этапах оказания стационарной медицинской помощи — в условиях отделения реанимации и интенсивной терапии (ОРИТ) и в терапевтических отделениях (ТО). Терапия метилпреднизолоном была проведена 54 пациентам, что составило 9% от общего количества госпитализированных больных в ФГБУ «ФЦМН» ФМБА России. В условиях ОРИТ терапия проводилась 28 пациентам, в условиях ТО — 26 больным, контрольную группу составили 14 пациентов. Метилпреднизолон вводили в суточной дозе 250 мг непрерывно внутривенно в течение трех суток, суммарная доза составила 750 мг. Результаты исследования показали достоверное уменьшение показателя летальности в группе, терапия метилпреднизолоном которым проводилась в ТО (7,7%) по сравнению с группой, в которой терапия проводилась в ОРИТ (67,9%) и контрольной группой (42,9%, $p < 0,001$). Также для группы с проведенной терапией в ТО была характерна меньшая частота проведения ИВЛ (в 2 (7,7%), 20 (71,4%) и 7 (50%) случаев, соответственно, $p < 0,001$). Таким образом, введение метилпреднизолона в условиях терапевтического отделения в качестве упреждающей противовоспалительной терапии способствует снижению показателей больничной летальности и частоты использования ИВЛ у пациентов с пневмонией, вызванной новой коронавирусной инфекцией COVID-19.

Ключевые слова: коронавирусная инфекция, COVID-19, глюкокортикостероиды, вирусная пневмония

The novel coronavirus SARS-CoV2 was first isolated and identified in Wuhan, China, in 2019. On March 11, 2020 WHO declared a pandemic of the novel coronavirus disease [1].

The excessive immune response to COVID-19 culminating in a cytokine release syndrome, also known as cytokine storm, plays the leading role in the pathogenesis of severe pneumonia caused by COVID-19. The devastating consequences of uncontrolled cytokine release include damage to the lungs, diffuse alveolar damage, acute respiratory distress syndrome (ARDS), and death [2–5].

So far, there is no effective etiotropic therapy against COVID-19. Improving oxygenation by prone positioning, oxygen therapy or mechanical ventilation, preventing and treating bacterial complications and using drugs to suppress the cytokine storm (glucocorticoids, inhibitors of proinflammatory factors and Janus-kinases) are the mainstay of anti-COVID-19 treatment [6–8].

Early reports on the benefits of glucocorticoid therapy in patients with COVID-19 were controversial [8-13]; however, later studies provided evidence of its efficacy [14, 15].

The aim of this study was to investigate the efficacy of methylprednisolone in reducing patient mortality in intensive care units (ICU) and medical wards.

METHODS

This study was a prospective quasi-experimental single-center open nonrandomized clinical trial. The study protocol was approved by the Academic Board of the Federal Center of Brain Research and Neurotechnology (FMBA, Russia) and the local Ethics Committee. The initial plan laid out in the first version of the protocol was that methylprednisolone would be administered only in an intensive care setting to eligible patients transferred to ICU from ER or a medical ward. Eligibility criteria

for transfer to ICU are specified in the guidance of the Russian Ministry of Healthcare (ver. 5 and 6). [16, 17]. However, due to the increasing number of patients admitted to medical wards with signs of lung damage similar to those in patients already transferred to ICU, the protocol was revised. Importantly, patients on the hospital floor had similar comorbidities to patients already transferred to ICU. So, considering the first-hand experience in treating patients with COVID-19, amendments were proposed to the first version, and the Academic Board of the Federal Center of Brain Research and Neurotechnology revised the protocol. The second version of the protocol permitted administration of methylprednisolone via continuous 3-day IV infusions using Infusomat/Perfusor Space systems in a medical ward setting.

From April 13, 2020 to May 25, 2020, 603 patients with community-acquired COVID-19-induced pneumonia were hospitalized to the Federal Center of Brain Research and Neurotechnology. Methylprednisolone therapy was administered to 54 patients (9% of all hospitalized patients). Group 1 ($n = 28$) included patients receiving methylprednisolone therapy in the ICU setting only between April 24, 2020 and May 6, 2020. Group 2 ($n = 26$) consisted of patients who received methylprednisolone in a medical ward setting between May 7, 2020 and June 12, 2020. The historical control group (group 3, $n = 14$) comprised patients hospitalized to the Federal Center of Brain Research and Neurotechnology from April 13, 2020 to April 23, 2020; these patients did not receive hormonal or other therapy for the cytokine storm (monoclonal antibodies, JAK inhibitors, etc.) and were comparable in terms of their clinical characteristics to the patients on methylprednisolone therapy.

The following inclusion criteria were applied:

1. Male and female patients aged over 18 years;

2. Positive PCR test results for SARS-CoV-2 RNA;

3. Clinical signs of pneumonia (fever >38.5 °C, respiration rate over 22 breaths per min, shortness of breath on exertion, $SpO_2 < 95\%$ at room air);

4. Chest CT findings suggestive of pneumonia.

Exclusion criteria:

1. Signs of bacterial or fungal infection confirmed by procalcitonin and/or presepsin test and full blood count;

2. HIV/AIDS;

3. Active or latent TB infection;

4. Congestive heart failure;

5. Recent myocardial infarction

6. Severely impaired liver and/or kidney function;

7. Recent intestinal anastomosis

8. Esophagitis, gastritis, active or latent peptic ulcer

9. Myasthenia gravis;

10. Glaucoma

11. Severe osteoporosis

12. Hypothyroidism

13. Psychiatric disorders

14. Poliomyelitis (except bulbar poliomyelitis and polioencephalitis)

15. BCG lymphadenitis;

16. Recent vaccination.

Continuous IV infusions of methylprednisolone (Solu-Medrol; 250 mg per day) were administered to the patients over the course of 3 days; the total dose was 750 mg. The patients were monitored for blood pressure and glycemia; proton pump inhibitors were prescribed for gastric protection. The patients also received standard therapy for COVID-19 recommended by the guidance of the Russian Ministry of Healthcare (ver. 5 and 6): antibacterial and detoxicating agents, antipyretic drugs, and anticoagulants [16, 17]. Antimalarial and anti-HIV medications

were not included in the regimen. Oxygen was delivered to patients with $SpO_2 < 93\%$ through nasal cannulas or a mask at 15 L/min.

Illness severity was assessed on the NEWS scale [18]; lung damage was evaluated based on the chest CT scans following the guidance [16, 17]. The efficacy of the administered therapy was determined based on the mortality rate; we also looked at the need for and duration of mechanical ventilation, the length of ICU and overall hospital stay. Body temperature dynamics were evaluated in groups 1 and 2 on days 3 and 5 after the beginning of methylprednisolone therapy; the respiration rate (RR) and SpO_2 were measured in group 1 and 2 patients who were not on MV. C-reactive protein (CRP) levels were measured to evaluate the severity of inflammation.

Statistical analysis

Categorical variables were compared using the chi square test; continuous variables were compared using the Kruskal-Wallis test (differences between all groups) and the Mann-Whitney U test (for groups 1 and 2).The Friedman test was applied to compare linked samples (SpO_2, RR and CRP before methylprednisolone therapy and on days 3 and 5 into therapy).To evaluate the effect of methylprednisolone on patient mortality adjusted for confounding factors (parameters that differed between the groups, including age, chronic heart failure, chronic renal failure, severity of lung damage on CT scans), binary logistic regression was applied. Quantitative variables are presented below as medians and upper and lower quartiles. All computations were performed in IBM SPSS ver. 16.0. The null hypothesis was rejected at $p < 0.05$. Two-tailed tests were used in all cases.

RESULTS

The basic characteristics of the patients included in the study are provided in Table 1. All groups were comparable in terms of demographics (age, sex), time from disease onset to hospitalization, time from hospitalization to the initiation of methylprednisolone therapy (for groups 1 and 2).

The analysis of comorbidities revealed that group 1 was dominated by patients with chronic heart failure (CHF) and chronic kidney disease (CKD); these conditions were observed in 39.3% ($p = 0.009$) and 25% ($p = 0.017$) of patients, respectively. For other comorbidities, no significant differences were detected between the groups. Similarly, no significant differences were observed between the groups in terms of presenting symptoms: the majority of patients presented with cough, fever and labored breathing. The severity of pneumonia on the NEWS scale was comparable between all patient groups. However, there were significantly more patients with severe lung damage in group 1 ($p = 0.012$). Thus, on admission the radiographic findings were indicative of a much more severe lung damage in group 1, which was also characterized by more frequent comorbidities, including CHF and CKD.

In group 1, 2 (7.1%) patients were transferred to ICU straight from ER; the remaining 26 patients were transferred from their medical wards to ICU due to disease progression, as recommended by the guidance [16, 17]. In group 2, only 2 patients (7.7%) were transferred to ICU after methylprednisolone therapy and then placed on MV. In spite of intensive care, these 2 patients died. Eight (57.1%) patients from group 3 were transferred from their medical wards to ICU and placed on MV; of them 6 (42.9%) individuals died.

Analysis of clinical outcomes (Table 2) revealed a significantly lower mortality rate in group 2 (2 (7.7%) cases), as compared to groups 1 (19 (67.9%) cases) and 3 (6 (42.9%) cases, $p < 0.001$). In group 2, ME was less frequent than in groups 1 and 3 (2 (7.7%), 20 (71.4%) and 7 (50%) patients, respectively, $p < 0.001$).

The longest ICU stay (median: 9 days) and the highest MV duration (median: 9 days) were observed in group 1 ($p = 0.025$ and $p = 0.023$, respectively). In group 2, these parameters equaled 5 and 5 days, respectively, and in group 3, 5 and 3 days, respectively. No significant differences were detected between the groups in terms of total hospital stay.

Considering that our groups differed in a number of factors that could potentially affect the outcome (CHF, CKD, severity of lung damage on a CT scan, age — all presenting a pronounced trend, see Table 1), we applied binary regression in order to make adjustments for these confounding factors. Results are provided in Table 3.

Adjusted for confounding factors, the odds of death in group 2 were significantly lower than in 2 other groups. Notably, the contribution of age was substantial whereas the contribution of other predictors was insignificant. Perhaps, CHF and CKD are more prevalent and lung damage visible on CT is more severe in patients of advanced age, i.e. these parameters are not significant outside the context of age. The overall quality of our regression model was satisfactory: Nigel-Kirk's pseudo-R-squared was 0.612, and the Hosmer-Lemeshow goodness of fit was 0.499.

Comparative analysis of clinical and laboratory parameters between the groups of patients receiving methylprednisolone therapy in ICU vs. a medical ward setting is provided in Table 4. By day 5 after methylprednisolone therapy was initiated, group 2 was dominated by patients without hyperthermia (23 (92%) cases), as compared to group 1, where only 13 patients (50%) ($p = 0.002$) had normal body temperature at this time point. Also, shortness of breath became less pronounced in group 2 on day 3 (end of methylprednisolone therapy): median RR was 19 breaths per min, whereas in group 1, RR was 24 breaths per min ($p = 0.043$). No significant differences in SpO$_2$ were detected between the groups.

Prior to methylprednisolone therapy, CRP levels were high in both groups treated with this drug (median 136 [94; 213] mg/L in group 1 and 148 [68; 183] mg/L in group 2). By day 3 into treatment, CRP levels started to decline, reaching 68 [41; 126] mg/L in group 1 and 52 [23; 142] mg/L in group 2; the differences between the groups were insignificant. On day 5, CRP levels differed significantly between groups 1 and 2 (68 [35; 210] mg/L and 29 [12; 52] mg/L, respectively, $p = 0.005$).

Table 1. Patient demographics

Parameter		Group 1 ($n = 28$)	Group 2 ($n = 26$)	Group 3 ($n = 14$)	Significance of differences, p
Sex	Male (%)	17 (60.7)	17 (65.4)	12 (85.7)	0.251
	Female (%)	11 (39.3)	9 (34.6)	2 (14.3)	
Age, years Median [Q1; Q3]		66 [58; 77]	59 [53; 70]	57 [49; 68]	**0.05**
Time from disease onset to hospital admission, days Median [Q1; Q3]		7 [5; 10]	7 [6; 9]	8 [3; 11]	0.831
Time from hospital admission to beginning of methylprednisolone therapy, days Median [Q1; Q3]		3 [2; 5]	3 [2; 6]	–	0.936
Comorbidities					
Hypertension (%)		18 (64.3)	12 (46.2)	8 (57.1)	0.405
Smoking (%)		2 (7.1)	2 (7.7)	1 (7.1)	1.00
Diabetes mellitus (%)		6 (21.4)	4 (15.4)	2 (14.3)	0.788
Past history of stroke or TIA (%)		4 (14.3)	2 (7.7)	1 (7.1)	0.662
Past history of myocardial infarction (%)		5 (17.9)	1 (3.8)	1 (7.1)	0.217
Obesity (%)		9 (32.1)	4 (15.4)	4 (28.6)	0.180
Asthma (%)		1 (3.6)	1 (3.8)	0	0.764
Chronic obstructive pulmonary disease (%)		3 (10.7)	2 (7.7)	0	0.454
Chronic heart failure (%)		11 (39.3)	4 (15.4)	0	**0.009**
Chronic kidney disease (%)		7 (25)	1 (3.8)	0	**0.017**
Presenting complaints					
Cough (%)		26 (96.3)	24 (92.3)	14 (100)	0.516
Fever (%)		27 (96.4)	25 (96.2)	14 (100)	0.449
Shortness of breath (%)		26 (96.3)	20 (76.9)	10 (71.4)	0.063
Severity on admission					
NEWS score Median [Q1; Q3]		5 [5; 7]	4 [2; 7]	4 [2; 6]	0.173
Lung damage on CT on admission	Grade 1 (%)	3 (10.7)	2 (7.7)	0 (0)	**0.012**
	Grade 2 (%)	2 (7.1)	12 (46.2)	3 (21.4)	
	Grade 3 (%)	11 (39.3)	10 (38.5)	7 (50)	
	Grade 4 (%)	12 (42.9)	2 (7.7)	4 (28.6)	

Intragroup comparisons of these parameters revealed that CRP ($p = 0.033$), SpO$_2$ ($p < 0.0005$) and RR ($p < 0.0005$) dynamics were significant in group 1. For group 1, only CRP dynamics were significant ($p = 0.023$), unlike RR and SpO$_2$.

DISCUSSION

This study investigated effects of methylprednisolone therapy at different stages of inpatient medical care. We found that administration of methylprednisolone in a medical ward setting aimed at preventing inflammation improves survival, reduces the frequency of patient transfer to ICU and the need for MV in patients with COVID-19-induced pneumonia. Methylprednisolone therapy delivered in the ICU setting did not have a significant effect on mortality (which was 67.9%), in comparison with the control group, whereas its early application in a medical ward setting prevented most patients from worsening, transfer to ICU and placement on MV, resulting in lower mortality.

Being a potent anti-inflammatory drug, methylprednisolone can block secretion of proinflammatory cytokines and accelerate resolution of pulmonary and systemic inflammation in patients with pneumonia [11, 19]. At the same time, some studies demonstrated that glucocorticoids hampered pathogen elimination from the organism and increased mortality in patients with other viral infections [11, 20]. However, there have been no studies so far addressing the use of the proposed methylprednisolone regimen against COVID-19.

There are a number of publications investigating the efficacy of glucocorticoid therapy in patients with COVID-19 progressed to pneumonia. Specifically, a retrospective cohort study conducted in patients with confirmed COVID-19 and ARDS revealed that methylprednisolone administered intravenously at 1–2 mg/kg per day for 5–7 days reduced the risk of mortality (23 deaths in 50 (46%) patients who received methylprednisolone vs. 21 deaths in 34 patients (61.8%) who

did not receive this drug) [21]. In another study conducted in 46 patients with severe COVID-19 progressed to respiratory failure, therapy with methylprednisolone was associated with better clinical benefits and reduced duration of the disease [22]. According to the Chinese Thoracic Society experts consensus, methylprednisolone should be administered at low to medium doses (≤ 0.5–1 mg/kg a day) [23]; it is reported that the most common methylprednisolone regimens in China are 40–80 mg of the drug per day for 3–6 days [24].

A study by Fadel Raef et al. [14] compared the effects of different methylprednisolone regimens in managing COVID-19: early (within 2 days after admission) vs. later (day 5 after admission therapy start. Methylprednisolone was delivered to patients at 0.5 to 1 mg/kg a day over the course of 3 days; the total daily dose was administered in two divided doses every 12 h. The study demonstrated the efficacy of early methylprednisolone therapy in achieving a primary composite endpoint (death from any causes + transfer to ICU + placement on ME). In the early therapy start group, the primary endpoint rate was 34.9%, whereas in the later start group, it was 54.3% ($p = 0.005$).

The methylprednisolone dosage and regimen used in our study differed from the cited studies: the drug was administered continuously at 250 mg per day for 3 days in a row; this allowed us to use a higher total methylprednisolone dose (750 mg).

Our study has a few limitations. Due its quasi-experimental design, there was no randomization and placebo control; the control group was formed based on the historical principle. Patients from group 1 were slightly older, had more comorbidities and more severe damage to the lungs on CT scans.

Summing up, this study demonstrates the need for a randomized double-blind placebo-controlled trial of the efficacy of methylprednisolone therapy in patients with pneumonia caused by the novel coronavirus infection. In our experience, preventive methylprednisolone therapy might be beneficial in terms of costs incurred by a medical facility in the absence

Table 2. Comparative analysis of clinical outcomes and some clinical variables

Parameter	Group №1 ($n = 28$)	Group №2 ($n = 26$)	Group №3 ($n = 14$)	Significance of differences, p
Death (%)	19 (67,9)	2 (7,7)	6 (42,9)	<0,001
ME (%)	20 (71,4)	2 (7,7)	7 (50)	<0,001
ME duration Median [Q1; Q3]	9 [6; 13]	5 [2; 7]	3 [1; 5]	0,023
Days in ICU Median [Q1; Q3]	9 [6; 17]	5 [2; 7]	5 [2; 6]	0,025
Total length of stay Median [Q1; Q3]	19 [12; 25]	16 [12; 19]	14 [6; 17]	0,074

Table 3. Binary logistic regression with confounding factors and a group factor, death is dependent variable. CI– confidence interval, OR– odds ratio. Significant predictors are highlighted. OR is not specified for the reference category in the case of categorial predictors

Predictor	Significance (p)	OR	95% CI for OR	
			Lower limit	Upper limit
Group 2	**0.003**			
Group 3	**0.002**	52.693	4.065	683.107
Group 1	**0.001**	47.824	4.690	487.640
CHF	0.165	0.202	0.021	1.929
CKD	0.140	6.191	0.549	69.790
Lung damage grade 1	0.654			
Lung damage grade 2	0.497	0.306	0.010	9.323
Lung damage grade 3	0.317	0.191	0.007	4.885
Lung damage grade 4	0.623	0.434	0.016	12.088
Age	**0.014**	1.104	1.021	1.194

Table 4. Comparative analysis of clinical and laboratory data between groups 1 and 2

Parameter	Group №1 (n = 28)	Group №2 (n = 26)	Significance of differences, p
Body temperature recovery on day 3 from therapy onset (%)	14 (51.9)	19 (73.1)	0.158
Body temperature recovery on day 5 from therapy onset (%)	13 (50)	23 (92)	0.002
RR before therapy Median [Q1; Q3]	24 [20; 28]	24 [22; 27]	0.754
RR on day 3 from therapy onset Median [Q1; Q3]	24 [20; 25]	19 [18; 20]	0.043
RR on day 5 from therapy onset Median [Q1; Q3]	20 [18; 30]	19 [18; 20]	0.117
SpO_2 before therapy, % Median [Q1; Q3]	90 [87; 94]	93 [90; 95]	0.340
SpO_2 on day 3 from therapy onset, % Median [Q1; Q3]	94 [89; 98]	95 [95; 97]	0.170
SpO2 on day 5 from therapy onset, % Median [Q1; Q3]	96 [84; 96]	97 [96; 98]	0.163
CRP before therapy Median [Q1; Q3]	136 [94; 213]	148 [68; 183]	0.436
CRP on day 3 from therapy onset Median [Q1; Q3]	68 [41; 126]	52 [23; 142]	0.307
CRP on day 5 from therapy onset Median [Q1; Q3]	68 [35; 210]	29 [12; 52]	0.005

of sufficient funding. The obtained data can be used in further studies looking into the effect of different therapeutic anti-COVID-19 regimens on public health budget at many levels.

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