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Comparative Analysis Methods in Optimizing Corticosteroid Therapy in Patients with Covid-19 and Diabetes Mellitus

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ABSTRACT

Background: The use of comparative analysis methods remains a relevant method of scientific knowledge in the context of studying the effectiveness of therapeutic measures for acute diseases during the epidemic. Among these diseases is Covid-19, on the evaluation of the effectiveness of the therapy of which this scientific study is directed.
Study purpose: To compare the efficacy and safety of the use of corticosteroids in patients with covid-19 and diabetes mellitus prescribed "by standards" and "calculation method".
Methods: Patients with novel coronavirus infection and diabetes were examined (n = 107). A comparative analysis was carried out according to the criteria: the duration of the period of intoxication, a blood test with a formula, glycemia, glycemic variability, CRP, D-dimer, transaminase.
Results: In all groups, redistributive leukocytosis was noted after the therapy. In patients receiving glucocorticoids at the rate of 0.1 mg/kg/day intramuscularly, the dynamics of the main indicators characterizing inflammation was comparable to those of patients with high recommended doses ($p<0.001$), and the dynamics of glycemic control indicators was significantly better. Although all groups of patients showed an increase in postprandial glycemia, only patients with high recommended doses had an increase to the level of indicators requiring a change in the dose of insulin administered.
Conclusions: For patients without diabetes, the dose of dexamethasone is prescribed according to the standards (median dose) regardless of body weight and comorbidities. In patients with diabetes, it is required in each case to determine the dose of dexamethasone individually at the rate of 0.1 mg / kg of body weight per day. It is this method of appointment that reduces the risk of adverse outcomes and ensures the achievement of positive dynamics of clinical and laboratory parameters.

Keywords: Comparative analysis, Covid-19, Diabetes mellitus, Corticosteroid therapy

INTRODUCTION

The method of comparative analysis is one of the most common in science in cases where the need for an optimal choice arises. This considers all the characteristics of the objects under study, as well as their comparison according to the required criteria. Despite the fact that the method is empirical, in epidemic conditions such as Covid-19, the method is one of the most accessible in assessing the effectiveness of ongoing therapy.

On March 11, 2020, the World Health Organization (WHO) declared the novel coronavirus infection caused by the SARS-CoV-2 virus and called COVID-19 a pandemic. Progressive systemic inflammation plays a significant role in the pathogenesis of COVID-19. The associated increase in cytokine production exacerbates the pathophysiology of severe COVID-19 (Shkarin et al., 2018; Chestnova and Podshibyakina, 2020; 2021). "Cytokine storm" increases the risk of developing acute respiratory distress syndrome and can lead to multiple organ failure (Sun et al., 2020). "Cytokine storm" and inflammation caused by an uncontrolled immunological response to the virus underlie the fatal complications of coronavirus infection, which requires the timely appointment of adequate therapy. And the most accessible method to reduce damage from cytokine activity is corticosteroids (Ivashkin et al., 2020).

Glucocorticosteroids (GCS) are one of the most popular anti-inflammatory drugs, with a long history of use. Corticosteroids have anti-inflammatory and immunosuppressive properties. When interacting with cytoplasmic receptors, corticosteroids form a complex that penetrates the cell nucleus and stimulates the synthesis of mRNA that induces the formation of proteins (in particular, lipocortin) that mediate cellular effects (Chestnova and Podshibyakina, 2021). The main effect of GCS is to reduce the level of circulating pro-inflammatory cytokines - interleukins (IL): IL-6, IL-1, IL-12, IL-18, tumor necrosis factor α and other inflammatory mediators, and therefore their use is potentially possible as therapeutic strategy for coronavirus infection (Ivashkin et al., 2020; Lin et al., 2020; Pedersen and Ho, 2020; Li et al., 2020).

It was noted that the risk group for a severe course of the disease includes people over 60 years of age and patients with chronic diseases of the respiratory system, cardiovascular system, diabetes mellitus, malignant tumors, and obesity.

Patients with diabetes mellitus are included in the risk group for a severe course of the disease, which requires the appointment of corticosteroid therapy. Today, dexamethasone (the RECOVERY study) has the greatest evidence base for COVID-19, but the issue of corticosteroid dosage has not been finally resolved. In diabetic patients, excessive intake of exogenous corticosteroids creates insulin deficiency and leads to increased glycemic levels and the risk of coma.

Now, the question of the dosage of corticosteroids has not been finally resolved. WHO and other organizations, based on the RECOVERY trials, recommend the use of low-dose corticosteroids (dexamethasone 6 mg). On the other hand, early studies in non-COVID-19 ARDS have shown higher

doses (dexamethasone 20 mg daily, methylprednisolone 1 mg/kg daily) to be effective. Also, the aborted studies of DexaCOVID and CoDEX in patients with COVID-19 ARDS used an initial daily dose of 20 mg dexamethasone. According to some authors, it is these doses of corticosteroids that have the full potential to modulate the immune response by saturating glucocorticoid GRα receptors (Horby et al., 2020; Makarova et al., 2021; Villar et al., 2020; Meduri et al., 2007).

Potential side effects of corticosteroids include hyperglycemia, which has a pronounced glucose toxicity, especially given the damage to the islet apparatus of the pancreas by coronovirus infection, which leads to an increase in blood sugar initially even in people who do not have carbohydrate metabolism disorders (Makarova et al., 2021; World Health Organization, 2020). However, the administration of corticosteroids in high doses, namely such doses are provided for by the latest clinical guidelines, has a downside. The use of high doses of corticosteroids, especially dexamethasone, suppresses not only the activity of the immune system, but also the function of the adrenal glands and the production of its own corticorsteroids (cortisone, cortisol), which under normal conditions are responsible for adaptation processes (axis - hypothalamus-pituitary-adrenal glands) (Leow et al., 2005). Metabolic imbalance due to impaired production of corticosteroids leads to a decrease and even depletion of adaptation reserves (body defenses), which is especially dangerous for patients with diabetes mellitus who initially have secondary immunodeficiency (Dibirov et al., 2005; Daryabor et al., 2020).

On the other hand, excessive intake of exogenous corticosteroids (contriansular hormones) creates insulin deficiency and leads to an increase in glycemia even in patients without diabetes, and in patients with diabetes, the risk of developing life-threatening conditions - ketoacidotic or hyperosmolar coma, followed by pulmonary edema and cerebral edema.

None of these known methods of corticosteroid therapy for COVID-19 dosing recommendations are not indicated in patients with diabetes mellitus. Namely, in this disease, it is necessary to especially consider all the risks of side effects of GCS therapy. Thus, the main unresolved problem remains - the optimal dosage of corticosteroids in the treatment of a new coronavirus infection in patients with diabetes mellitus.

STUDY PURPOSE

Compare the efficacy and safety of using corticosteroids in patients with covid-19 and diabetes mellitus prescribed “according to standards” and “calculation method”.

DESIGN

The study was conducted based on the Endocrinology Department of City Clinical Hospital F.I. Inozemtsev (Moscow) in 2022.

Ethical Consideration

The Ethics Committee of the Medical Institute of the RUDN University (Protocol No. 5 dated March 17, 2022) approved the research.

Table 1. Clinical characteristics of the groups.

	Group 1 (n = 35)	Group 2 (n = 38)	Group 3 (n = 34)
Age (years)	65.16±3.97	59.58±10.72	68±11.79
Gender (male/female)	19/16	22/16	18/16
BMI (kg/m2)	31.85±5.15	30.07±3.94	31.17±5.57
Dose of dexamethasone (mg/kg/day)	0.11±0.04	0.28±0.08	0.12±0.02
Length of stay in hospital (days)	6.5±3.23	7.31±2.15	6.28±2.1
P	0.28	0.18	0.04

Note: P values <0.05 were taken as the level of statistical significance.

MATERIALS AND METHODS

A study was conducted to evaluate the efficacy and safety of using various doses of corticosteroids in patients with a new coronavirus infection and diabetes mellitus treated in a therapeutic department (n = 107). All patients were divided into 3 groups. In group 1 (n = 35), patients received dexamethasone at a dosage of 0.1 mg/kg once a day, intravenously (i.v.) in the morning; in the 2nd group (n = 38), patients received dexamethasone at a dosage of 20 mg 2 times a day intravenously in the morning and evening (more than 0.2 mg/kg/day); in the third group (n = 34), patients received dexamethasone at a dosage of 0.1 mg/kg once a day in the morning intramuscularly (IM). Clinical characteristics of patients in the examined groups are presented in Table 1.

All groups of patients received interleukin-6 inhibitors (tocilizumab, levilimab), anticoagulant therapy with low molecular weight heparins in accordance with interim clinical guidelines for the treatment of a new coronavirus infection.

Instruments and Data Collection Procedure

All patients during their stay in the hospital repeatedly underwent laboratory examinations at admission and at discharge (clinical blood test, C-RP, D-Dimer, ALT, AST, fasting glycemia, postprandial glycemia, glycemia variability.)

A comparative analysis was carried out according to the criteria: the duration of the period of intoxication, a blood test with a formula, glycemia, glycemic variability, CRP, D-dimer, transaminase. For analysis STATISTIC 10.0 computer program was used (Matematica®, Matlab®, HarvardGraphics® StatSoft. The basic methods were linear descriptive statistics (DescriptiveStatistics) with a calculation of the correlation of average standard deviations (corrs / means / SD).

RESULTS

All patients during their stay in the hospital underwent regular monitoring of laboratory parameters and in table 1 we present the data of laboratory tests for each group at admission (study 1) and at discharge (study 2) (table 2).

Table 2. Dynamics of laboratory parameters at admission and before discharge..

Index	Group 1 (n = 35)		Group 2 (n = 38)		Group 3 (n = 34)	
	1 research	2 research	1 research	2 research	1 research	2 research
Leukocytes (109/ml)	8.37±4.72	14.22±5.02	5.18±0.98	8.05±0.41	5.83±2.84	9.03±2.75
P	0.0001		0.0001		0.0001	
Fasting glycemia (mmol/l)	7.72±0.72	8.65±2.71	8.93±2.49	13.04±4.32	6.52±2.36	8.36±1.37
P	0.05		0.0001		0.0002	
Postprandial glycemia (mmol/l)	8.31±2.17	13.48±3.98	10.53±4.92	25.15±5.64	8.37±2.36	11.93±5.22
P	0.0001		0.00001		0.0001	
Glycemic variability (mmol/l)	2.93±1.97	5.21±2.89	4.85±3.15	7.89±3.92	3.47±2.06	6.35±1.22
	0.000		0.0003		0.0001	
CRP (mg/l)	81.78±32.89	17.24±10.51	121.01±41.48	19.42±8.17	103.76±65.37	12.23±4.52
P	0.0001		0.00001		0.00001	
D-dimer (ng/ml)	2710.45±1649.87	518.01±156.74	1369.75±108.17	439.75±130.72	1977.65±807.37	530.83±152.04
P	0.00001		0.00001		0.00001	
ALT (u/l)	32.75±12.12	56.75±31.74	41.03±18.53	90.25±32.92	38.17±18.41	55.51±16.09
AST (u/l)	26.62±15.74	30.25±18.11	53.02±23.07	54.92±42.46	31.67±13.88	30.83±10.48
P	0.0001		0.0001		0.001	

Note: P values <0.05 were taken as the level of statistical significance.

In group 1, there was a statistically significant increase in the level of leukocytes at the end of the period of stationary observation by 41% (P -0.0001); in group 2 - by 36% (P -0.0001); in group 3 - by 35% (P -0.0001). Fasting glycemia in group 1 patients increased by 22% (P = 0.0002); in group 3 - by 12% (P = 0.05); in group 2 - by 32% (P = 0.0001). Postprandial glycemia increased in the group 2 times by 58.1% (P = 0.00001); in group 1 - by 38% (P = 0.0001); in group 3 increased by 28% (P = 0.0001).

The indicator of glycemic variability increased maximum in group 2 - by 61% (P = 0.0003); in group 1 - by 55% (P = 0.0001); in group 3 - by 54% (P = 0.0001).

In group 2, the level of ALT and AST increased by 31.1 and 16.6%, respectively (P = 0.0001); in group 1, the level of ALT and AST increased by 42.3% and 12%, respectively (P = 0.0001); in group 3 - by 31.2% and 3.7% (P = 0.001).

In patients of group 2, there was a decrease in the level of D-dimer by 67.9% (P<0.0001); in group 1 by 80.9% (P<0.0001); in group 3 - by 73.2 (P<0.0001).

The decrease in the level of CRP did not have significant differences in the compared groups. In patients with diabetes mellitus in group 2 by 84.3% (P<0.0001); in group 1 - by 78.9% (P<0.0001); in group 3 - by 88.2 (P<0.0001).

In all groups, after the therapy, redistributive leukocytosis was noted. In patients receiving high therapeutic doses (group 2), the initially suppressed production of leukocytes was activated and reached the normative values (p<0.001), and the indicators were comparable to those of group 3, in which patients received glucocorticoids at a lower dose (0.1 mg/day). kg/day) intramuscularly (p<0.001).

The decrease in the level of C-reactive protein, one of the main criteria for a cytokine storm in a new coronavirus infection, did not differ significantly between groups, as did an increase in the level of leukocytes and a decrease in the level of D-dimer.

In all groups of patients, an increase in postprandial glycemia was observed, and in group 2 it reached the level of indicators characteristic of the development of a ketoacidotic state and required emergency intervention with an increase in the dose of insulin administration. In patients of this group, optimal correction of hyperglycemia was achieved, which required the transition to an intensive regimen of insulin therapy in 100% of patients. In group 3, only in 47% of cases, and in group 1 - in 78% of patients.

Thus, the optimal doses of dexamethasone therapy in patients with diabetes mellitus were determined, taking into account the effectiveness of influencing the main parameters of inflammation and side effects from corticosteroid therapy.

DISCUSSION

Currently, there is no individual approach to therapy in prescribing corticosteroids for a patient with Covid-19 and diabetes mellitus (a dose is prescribed without taking into account the patient's weight, the presence

of metabolic disorders, namely diabetes mellitus). The consequences of the influence of the prescribed dose on the state of the regulatory system (hypothalamus - pituitary gland - adrenal glands) are not taken into account. The consequences of the influence of the prescribed dose on the hormone-producing ability of the adrenal glands are not taken into account. And doctors are well aware that at the maximum recommended doses of glucocorticoids (20 mg), the level of glycemia increases, which in patients with diabetes can lead to uncontrolled hyperglycemia, ketoacidosis.

As a result of the study, using the methods of comparative analysis, the effectiveness of various options for the treatment of corticosteroids in patients with diabetes mellitus was evaluated. The effectiveness of corticosteroids in anti-inflammatory therapy and the reduction of the manifestations of the "cytokine storm" was sufficient not only at high doses of dexamethasone recommended by the standards, but also in patients who received the dose calculated during the study - 0.1 g / kg / day. A decrease in the total daily dose of dexamethasone had a positive effect on glycemic control.

With standard glucocorticoid therapy, all patients with DM were transferred to an intensive regimen of insulin therapy, insulin doses were increased by an average of 57% compared with the starting ones, when prescribing an individually calculated dose of glucocorticosteroids, the possibility of combination therapy remained and the doses of insulin administered increased by an average of 37% with intravenous and 22% with intramuscular corticosteroids. Patients who received dexamethasone at a rate of about 0.1 U/kg (8-12 mg) once a day intravenously or intramuscularly had the most satisfactory indicators of postprandial glycemia and glycemic variability, which is a very important criterion for patients with diabetes mellitus, and reduces the number of complications associated with hyperglycemia.

CONCLUSION

For patients without diabetes, the dose of dexamethasone is prescribed according to standards (average dose) regardless of body weight and concomitant diseases. In patients with diabetes, it is necessary to determine the dose in each case dexamethasone individually at the rate of 0.1 mg/kg of body weight per day. Exactly this method of administration reduces the risk of adverse outcomes and to ensure the achievement of positive dynamics of clinical and laboratory indicators, and, ultimately, reduce mortality and shorten the time recovery.

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