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EVALUATION OF THE EFFECTIVENESS OF RUTAN IN THE COMPLEX THERAPY OF COVID-19 IN CHILDREN

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Abstract. The global pandemic of coronavirus disease 2019 (COVID-19) presents an unprecedented challenge to public health, social and economic life [1, 2]. Despite the numerous drugs proposed for etiotropic treatment, there are currently no unequivocally proven effective drugs for adults and especially for children. The study is devoted to the study of the properties of the drug Rutan and the evaluation of its effectiveness in the complex therapy of COVID-19 in children aged 6-18 years.

The study included the study and analysis of the properties of the drug Rutan, its effectiveness in the complex therapy of COVID-19 in children aged 6-18 years. An open, controlled, comprehensive, randomized clinical laboratory study was conducted.

Clinical studies were conducted on 201 patients with mild and moderate forms of COVID-19 aged 6-18 years who were treated at the Zangiota 1 specialized clinic. Rutan 25 mg was used in the complex therapy of 101 children aged 6-18 with COVID-19. 100 patients who received only complex therapy served as a comparison group. It was found that Rutan 25 mg was well tolerated and harmless to patients, with no side effects. A pronounced clinical and significant antiviral effect was shown in patients with mild and moderate disease. After suffering COVID-19, in 30.7% of cases, post-covid symptoms are formed, mainly reflecting asthenic-vegetative, inflammatory-painful, catarrhal-respiratory manifestations within 4-6 months. In children treated with Rutan 25 mg, the frequency of post-covid manifestations was significantly less than in children in the control group ($P<0.05$).

Keywords: COVID-19, children 6-18 years old, Rutan 25 mg, antiviral efficacy

INTRODUCTION. The global pandemic of coronavirus disease 2019 (COVID-19) presents an unprecedented challenge to public health, social and economic life [1, 2]. The etiological agent of COVID-19 is a new member of the Coronaviridae family, which is closely related to severe acute respiratory syndrome coronavirus (SARS-CoV) and has been named SARS-CoV-2 by the taxonomy of viruses [3].

At the initial stage of the COVID-19 pandemic, there was a low incidence among children, which was due mainly to asymptomatic or mild disease in children [16, 23]. It should also be taken into account that the closure of schools and preschool institutions occurred in most places at the same time, the closest contacts began to be limited to households, which reduced the opportunities for children to become infected in the community [22]. However, studies in the UK among 2 million children who had signs of COVID-19 identified 8 children with symptoms similar to shock syndrome in Kawasaki disease [25].

The worldwide spread of SARS-CoV-2 coronavirus infection determines the need to study the clinical features, complications, extrapulmonary manifestations and long-term consequences of

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the infection in children. While many studies in adult patients have been described, there are limited data analyzing the clinical course of the disease in pediatric patients infected with SARS-CoV-2 [1, 3, 9, 10, 18, 19, 20, 22, 25, etc.].

The course of COVID-19 in children in Uzbekistan is comparable to foreign data. However, the risk of developing a severe course of COVID-19 is typical for children with comorbidities. Currently, the most vulnerable to the new coronavirus are children with severe oncological, neurological and cardiovascular pathologies, who experience rapid decompensation of the underlying disease against the background of COVID-19 [10]. Proper organization of departments for the treatment of children infected with COVID-19 in a hospital, taking into account the characteristics of the course of the disease, possible critical complications and their adequate intensive care, will increase the effectiveness of measures aimed at combating the pandemic.

COVID-19 in children has features compared to other SARS. However, the principles of therapy are similar and involve taking into account the severity of the disease and the early start of etiotropic treatment using the available arsenal of antiviral drugs approved for use in children and having an evidence base [11,12].

The clinical picture of the disease in children, as well as in adults, is dominated by fever and respiratory syndrome. At the same time, the experience of different countries during the COVID19 pandemic shows that children have a smoother course of the disease compared to adults, lower respiratory tract damage in the form of viral pneumonia is less common, symptoms are usually mild, and deaths are extremely rare. However, it is children of any age that should be the focus of special attention, since they play a huge role in the spread of the disease [15, 19].

A feature of the course of COVID19 in children is the predominance of intoxication and respiratory syndromes, in most children the mild form prevails, the moderate form and isolated cases with multisystem inflammatory syndrome are less common. Studies by a number of scientists describe that in most children with monocoronavirus infection, the acute onset of the disease prevailed. An increase in body temperature to febrile numbers at the onset of the disease was observed in 52.5% of children. The duration of the febrile period in 72.5% of children was 1-2 days. Children noted cough (100%), rhinitis (94.8%), laryngotracheitis with laryngeal stenosis of the 1st degree (52.5%), and hard breathing during auscultation (65%) [17].

Despite the lower prevalence of COVID-19 in children during the initial stages of the pandemic, by mid-2021 there was a sharp increase in the incidence among children. Mortality in this age group is low and usually occurs in patients with underlying disease and morbid obesity. It has been noted that COVID-19 can cause symptoms in children in two stages. In the first week, upper and lower respiratory symptoms may occur, which are of lesser severity and prevalence than in adults. But 2-3 weeks after infection, symptoms of a polysystemic lesion may appear. The most common indications for hospitalization are fever, rash, and breathing problems. Kawa-COVID-19 is likely a novel systemic inflammatory syndrome temporally associated with SARS-CoV-2 infection in children. Further prospective international studies are needed to confirm these findings and better understand the pathophysiology of Kava-COVID-19 [20, 24]. Some researchers are of the opinion that the pathogenesis of Kava-COVID-19 is based on the reaction of the human immune system, which attacks and kills virus-infected cells like a cytokine storm [4, 25].

The picture of the disease and the frequency of infection have changed significantly after the start of mass immunoprophylaxis of COVID-19, however, it is necessary to continue the implementation of all measures aimed at reducing the spread of a new coronavirus infection. A special place should be given to the development of a mixed infection of COVID-19 with other acute respiratory viral infections, including

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influenza. It was found that most often the formation of a severe course of COVID-19 was observed in children with mixed infections [13,14]. In this regard, a separate task should be considered the maximum intensification of work to increase influenza vaccination coverage (especially among patients at risk) in the context of the ongoing COVID-19 pandemic, which will not only significantly reduce the incidence of influenza, but will also help reduce the incidence of severe forms of the disease in mixed infections [13,14].

Thus, the pandemic potential of COVID-19 requires constant monitoring for timely detection and prediction of possible adaptation and evolution of the virus, changes in virulence and pathogenicity. These factors will ultimately affect mortality rates and morbidity prognosis. Research is also needed to identify effective drugs for the treatment of COVID-19, especially for children.

In the present studies, a study was made of the structural features of polyphenols, antiviral activity in in vitro and in vivo models in the experiment, preclinical and clinical studies of the drug, which made it possible to recommend it for use in the treatment of coronavirus infection COVID-19 in adults and children.

PURPOSE OF THE RESEARCH: Evaluation of the clinical, laboratory and antiviral efficacy of Rutan 25 mg in the complex therapy of COVID-19 in children aged 6-18 years.

MATERIALS AND RESEARCH METHODS.

To achieve this goal, 201 patients with COVID-19 aged 6 to 18 years were examined. 101 patients received standard treatment according to the protocol [5, 6] and additionally Rutan 25 mg x 2 times a day as an antiviral drug, 100 patients - the control group, received only standard therapy according to the protocol. According to the age factor, the patients were divided into 3 groups (6-10 years old, 11-14 years old and 15-18 years old). All patients underwent daily monitoring of the clinical symptoms of the disease, dynamic analysis (upon admission and before discharge from the hospital) of a number of laboratory parameters (C-reactive protein, procalcitonin, ferritin, D-dimers, IL6, etc.), as well as virological studies with the determination of the COVID-19 virus in the nasal secretion of patients and its daily dynamic testing until the patients are discharged from the hospital (until it disappears). After discharge from the hospital, to assess the condition and well-being of patients and analyze possible post-COVID disorders, a telephone survey of 127 convalescents was conducted using a specially designed questionnaire that reflects possible disorders and post-COVID conditions - long COVID.

The results of the study were subjected to statistical processing with the determination of p-Value.

RESULTS AND DISCUSSION.

During the study, it was found that the drug Rutan at a dose of 25 mg in the general population of children aged 6-18 years does not have side effects when used in the complex therapy of children with COVID-19, does not have antagonistic effects when used together with the drugs indicated in protocols for the treatment of this disease in children. The results of treatment of patients of the main and control groups were analyzed, taking into account the age of the patients. In no case was there an individual intolerance to Rutan in the main group of patients, regardless of their age. We also established the absence of side effects from the use of Rutan in each of the three age groups and the absence of any reactions when using this drug in the complex therapy of patients with COVID-19, which was compared with the control group of patients who did not receive Rutan in the basic standard therapy. . Based on the study, it was concluded that Rutan is harmless, does not have side effects in the treatment of patients with COVID-19 in children in the age groups of 6-18 years.

An analysis was made of a number of clinical symptoms of the disease and laboratory parameters that are the most informative according to the protocol for managing patients with COVID-19, which included the determination of CRP (C-reactive protein), procalcitonin, ferritin, IL6, general laboratory tests that mainly reflect inflammation processes in the body in examined individuals and their dynamic study.

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According to the results of the study of patients of the main and control groups, there was no significant anti-inflammatory effect of Rutan 25 mg ($p>0.05$). At the same time, the analysis of a number of clinical symptoms of the disease in patients of the compared groups, both in the general population aged 6-18 years, and when ranking by age, revealed a significant efficacy of Rutan 25 mg. This was especially noticeable in such indicators as the relief of hyperthermia, a decrease in the severity of cough, shortness of breath, restoration of appetite, a decrease in weakness, lethargy and other manifestations of the disease compared with the control group of patients (Table 1). Even more significant were the differences in the rate of relief and the severity of clinical symptoms according to the results of treatment in patients of the main group and control when ranking them by age (6-10 years, 11-14 years and 15-18 years).

It was found that in the group of children aged 6-10 years, the relief of these symptoms of COVID-19 was significantly faster compared with patients aged 11-15 years ($P<0.05$). When compared with the adolescent group of children (15-18 years old), we did not find such differences. However, for a number of symptoms (sore throat, abdominal pain, malaise, etc.), there was a faster relief in children aged 6-10 years compared with older age groups ($P<0.05$). This may indicate that when distributed by body weight in the younger age group, the dose of Rutan 25 mg is more effective than the same dose in children of older age groups with a correspondingly larger body weight.

Additionally, the analysis of viral load indicators and its dynamics in patients of the main and control groups was carried out in order to determine the antiviral effect of the drug Rutan 25 mg when taken 3 times a day in children in different age groups.

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Table 1.

The frequency of occurrence of a number of clinical symptoms in children aged 6-18 years of the main and control groups upon admission to the hospital and before discharge

Upon admission to the hospital	Main (n=101) Abs	%	Control (n=100) Abs	%	**P -Value**	Before discharge	Main (n=101) Abs	%	Control (n=100) Abs	%	**P -Value**
Weakness, lethargy	101	100,0	100	100,0	=0,00	Weakness, lethargy	91	90,2	96	96,0	=0,72
Dry cough	96	95,0	100	100,0	=0,15	Dry cough	83	82,2	85	85,0	=0,80
Cough wet	10	9,9	0		=0,04	Cough wet	12	11,9	10	10,0	=0,75
Hyperthermia	98	97,0	95	95,0	=0,56	Hyperthermia	5	4,9	22	22,0	**=0,02**
Malaise	101	100,0	100	100,0	=0,00	Malaise	15	14,8	22	22,0	**=0,36**
Dizziness	39	38,6	44	44,0	=0,65	Dizziness	15	14,8	18	18,0	**=0,31**
Pain when swallowing	69	68,3	68	68,0	=1,00	Pain when swallowing	5	4,9	17	18,0	**=0,07**
pharynx, redness, grainy	81	80,2	90	90,0	=0,21	pharynx, redness, grainy	29	28,7	42	42,0	**=0,21**
Pronounced sweating	101	100,0	100	100,0	=0,00	Pronounced sweating	44	43,6	45	45,0	=0,92
Pain with deep inhalation/exhalation	42	41,6	15	15,0	=0,0064	Pain with deep inhalation/exhalation	0		8	8,0	**=0,08**
Headache	89	88,1	76	76,0	=0,15	Headache	2	2,0	8	8,0	**=0,29**
Loss of appetite	91	90,1	83	83,0	=0,33	Loss of appetite	8	7,9	7	7,0	=0,67
Diarrhea	12	11,9	2	2,0	=0,09	Diarrhea	0		0		=0,00
Nausea, vomiting	15	14,8	12	12,0	=0,74	Nausea, vomiting	0		2	2,0	**=0,32**
Pain in muscles and bones	89	88,1	83	83,0	=0,53	Pain in muscles and bones	2	2,0	1	1,0	=0,49
Pain in the right hypochondrium	5	4,9	5	5,0	=1,00	Pain in the right hypochondrium	0		0		=0,00
Loss of taste and smell	17	16,8	2	2,0	=0,02	Loss of taste and smell	33	32,7	33	33,0	=0,92

Note: p-Value values from 1.0 to 0.5 - non-significant differences (P>0.05); from 0.5 to 0.1 - medium degree of significance (P<0.05), less than 0.1 - high degree of significance of differences (P<0.01-0.001).

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Analysis of the dynamics of the virus in the nasal secretion in patients aged 6-18 showed significant differences in patients of the comparison groups (Table 2). So, according to the results of the study of the virus on the 5th day of sampling in the group of children who received Rutan, the virus was practically not detected, while in the control group who did not receive this drug, the indicated indicator was 4 times higher than that in the main group (P< 0.05).

table 2

Dynamics of virus content in nasal secretion in patients of the main and control groups (n=196)

Research days	**Rutan n=98**	**No Rutan n=98**	**p-Value**
Day 1	69,6%	61,2%	=0,3
Day 2	51,0%	47,9%	=0,6
Day 3	24,5%	22,4%	=0,5
Day 4	14,4%	13,2%	=0,8
Day 5	0,2%	0,8%	=0,05

Note: p-Value – reliability of differences between the compared groups

The results obtained showed that the use of the drug Rutan 25 mg in the complex therapy of children aged 6-18 years with COVID-19 is characterized by the absence of side effects, good tolerance and harmlessness for the body of this group of patients and has a pronounced clinical and significant antiviral effect in patients with mild and moderate course of the disease.

Research shows that many people who recover more than 12 weeks after being infected with COVID-19 experience a post-COVID-19 condition (also known as long-term COVID). A post-COVID-19 condition is not COVID-19. Symptoms can be very different from those that occur with the initial infection. This refers to the long-term effects that some people experience after being infected with COVID-19 [7, 8, 26].

The condition can affect both adults and children. Sometimes symptoms may disappear and reappear without explaining another diagnosis. Some patients report that overexertion (both mental and physical) can worsen the condition [7, 8].

In this regard, we analyzed the possible post-COVID conditions in the examined children after discharge from the hospital within a period of 4 to 6 months. A telephone survey of 201 previously examined children managed to interview 127 (63.2%) children, of which 62 children were from the main group, who received, in addition to the complex therapy of the disease according to the protocol of management, the drug Rutan 25 mg 2 times a day while they were on treatment in the specialized infectious diseases clinic "Zangiota 1" with mild and moderate course of COVID-19, 65 children from the comparison group who received only protocol therapy without Rutan. The list of the questionnaire was compiled on the basis of the symptoms of the disease that prevailed during the illness, and was also supplemented with the most frequently recorded post-COVID manifestations described in the literature. In the main group, there were 28 (45.1%) girls, 34 (54.9%) boys, in the control group 28 (43.1%) and 37 (56.9%), respectively. The groups were randomized, which determined the reliability of the data obtained.

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According to the results of the study, it was found that in children who received the drug Rutan in the complex therapy of patients who were treated for this disease in a specialized clinic Zangiota 1, in 13 cases there were a number of clinical symptoms of the disease, such as prolonged weakness, fatigue, acute respiratory viral infections in terms of from 1 month after suffering COVID-19.

Among patients in the control group who did not receive Rutan, 26 patients with post-covid symptoms were noted, which is 2 times more than among patients who received Rutan 25 mg 2 times a day in complex therapy ($P<0.05$). Also, it should be noted that patients in the control group had not only a high frequency of post-COVID conditions and symptoms, but also their greater severity and variety: weakness, lethargy, frequent acute respiratory viral infections, abdominal pain, prolonged cough, fatigue, loss of appetite, changes in taste preferences, loss of taste and smell, etc.

We combined a number of indicators into groups according to syndromes: vegetative-asthenic syndrome (irritability, nervousness, lag in school, weakness, fatigue, difficulty sleeping, dizziness, nausea, weight loss, hair loss, sweating); respiratory catarrhal (ARVI or Covid within 3 months after discharge, shortness of breath, chest pain, lack of air, nasal congestion, runny nose, sore throat, cough, hoarse voice, chills); inflammatory pain (pain in the muscles, headache, pain in the eyes, swelling of the face, pain in the abdomen, pain in the right hypochondrium, heaviness in the arms and legs, pain in the joints); other symptoms (loss of smell and taste, allergies, plaque on the tongue, diarrhea, vomiting, thrombosis, heart problems, hearing problems, memory impairment).

Based on the results of the survey, it was found that the manifestations of astheno-vegetative (14 patients of the main group - 22.6% and 20 children of the control group - 30.8%, respectively) and inflammatory-pain syndrome (4 children from the main group - 6, 4% and 9 children from the control group - 13.8%, respectively) in patients of the compared groups of patients. The frequency of detection of catarrhal respiratory syndrome was detected in 5 patients of the main (8.1%) and 5 children (7.7%) of the control group ($P>0.05$). Analysis of the frequency of post-covid conditions in children depending on gender did not show significant differences in boys and girls ($P>0.05$).

An analysis of the frequency of detection of post-COVID states in different age groups showed that in the main group of patients, post-COVID states were more often recorded in patients of the adolescent group aged 15-18 years, in the group of children aged 6-10 and 11-14 years, the frequency of post-COVID states was less common. In the control group of children who did not receive Rutan, the frequency of occurrence of post-covid symptoms was most often recorded in the group of children aged 6-10 and 15-18 years, in the group of 11-14 years these symptoms were less common.

The results of a clinical study of the drug in children showed that the use of the drug Rutan 25 mg in the complex therapy of children aged 6-18 years with COVID-19 is characterized by the absence of side effects, good tolerance and harmlessness for the body of this group of patients and has a pronounced clinical and significant antiviral effect. in patients with mild to moderate disease.

It has been shown that post-COVID-19 symptoms develop in 30.7% of cases after suffering from COVID-19, mainly reflecting asthenovegetative, inflammatory-painful, catarrhal-respiratory manifestations within 4-6 months. In children receiving Rutan 25 mg, the frequency of post-covid manifestations was significantly less than in children in the control group..

CONCLUSIONS:

1. The domestic drug Rutan 25 mg in the complex therapy of children aged 6-18 years with COVID-19 is characterized by the absence of side effects, good tolerance and harmlessness for the body of this group of patients;
2. Rutan has a pronounced clinical and significant antiviral effect in patients with mild and moderate course of the disease, and is also much cheaper in cost compared to existing antiviral drugs, which makes it the most preferred option in the treatment of children with COVID-19 and ARVI ;
3. In children who have recovered from COVID-19 in mild and moderate form, in 30.7% of cases, post-covid symptoms are formed, mainly reflecting asthenic-vegetative, inflammatory-painful, catarrhal-respiratory manifestations in terms of up to 4-6 months. after an illness; in children treated with Rutan 25 mg, the frequency of post-covid manifestations was recorded much less frequently than in children in the control group ($P<0.05$).

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