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Hydroxychloroquine sulfate Normal treatment 2019 Coronavirus disease (COVID-19)patient initial research

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[Summary] purpose: Preliminary evaluation hydroxychloroquine sulfate Normal treatment 2019 Coronavirus disease (COVID-19) Efficacy and safety of patients. **method:** collect 2020 year 2 month 6 To 25 Day at the Shanghai Public Health Clinical Center hospitalization 30 Ordinary cases COVID-19 Diagnosed patients. patient 1: 1 Randomly assigned to the test group and control group. The control group received conventional treatment, the test group was treated with hydroxychloroquine sulfate on the basis of conventional treatment (400 mg , 1 Times / d , Treatment for 5 d)treatment. The first two groups were compared treatment 7 Indicators days throat virus nucleic acid negative rate. Study was approved by the Shanghai Public Health Clinical Center Ethics Committee, and registered (NCT04261517). **result:** During treatment, the test group 1 Patients who develop severe. After the first enrollment 7 Day, the experimental group 13 example(86.7%) And the control group 14 example(93.3%) Throat virus nucleic acid test is negative ($P > 0.05$). in 2 Visit week period, all nucleic acid detection swabs are subject to negative, wherein negative nucleic swab test group for the first time after admission 4 (1 to 9) Days of the control group 2 (1-4) Days, no statistically significant difference ($U = 83.5$, $P > 0.05$). The first test group after admission 1 (0-2) Day temperature returned to normal, the control group after admission 1 (0-3) Day temperature returned to normal. On the imaging test group 5 example(33.3%) And control group 7 example(46.7%) Were admitted to hospital 3 d After a review of progress emerged, all patients in the subsequent review of the lesions were prompted improved. Experimental and control groups, respectively 4 example(26.7%)with 3 example(20.0%) Had transient diarrhea and liver dysfunction and other adverse reactions ($P > 0.05$). **In conclusion:** Currently Normal COVID-19 Patients with good prognosis, negative rate of virus research, aggravation rate of the primary endpoint of efficacy of the drug is difficult to compare. Follow-up studies need to identify more appropriate to carry out the crowd and end points, and give full consideration to the feasibility of the sample size and other tests.

[Key words] Severe acute respiratory syndrome coronavirus 2; 2019 coronavirus disease; pneumonia novel coronavirus; hydroxychloroquine sulfate; treatment; Security

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A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19)

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[Abstract] Objective: To evaluate the efficacy and safety of hydroxychloroquine (HCQ) in the treatment of patients with common coronavirus disease-19 (COVID-19). **Methods:**
We prospectively enrolled 30 treatment-naïve patients with confirmed COVID-19 after informed consent at Shanghai Public Health Clinical Center The patients were randomized 1:. 1 to HCQ group and the control group Patients in HCQ group were given HCQ 400 mg per day for. 5 days plus conventional treatments, while those in the control group were given conventional treatment only. The primary endpoint was negative conversion rate of COVID-19 nucleic acid in respiratory pharyngeal swab on days 7 after randomization. This study has been approved by the ethics committee of Shanghai public health clinical center and registered online (NCT04261517).

Results: One patient in HCQ group developed to severe during the treatment. On day 7, COVID-19 nucleic acid of throat swabs was negative in 13 (86.7%) cases in the HCQ group and 14 (93.3%) cases in the control group ($P > 0.05$). The median duration from hospitalization to virus nucleic acid negative conservation was 4 (1-9) days in HCQ group, which is comparable to that in the control group [2 (1-4) days, (U = 83.5, $P > 0.05$)]. The median time for body temperature normalization in HCQ group was 1 (0-2) after hospitalization, which was also comparable to that in the control group 1 (0-3). Radiological progression was shown on CT images in 5 cases (33.3%) of the HCQ group and 7 cases (46.7%) of the control group, and all patients showed improvement in follow-up examination. Four cases (26.7%) of the HCQ group and 3 cases (20%) of the control group had transient diarrhea and abnormal liver function ($P >$ 0.05). **Conclusions:** The prognosis of common COVID-19 patients is good. Larger sample size study are needed to investigate the effects of HCQ in the treatment of COVID-19. Subsequent research should determine better endpoint and fully consider the feasibility of experiments such as sample size.

[Key words] Severe acute respiratory syndrome coronavirus 2; Corona virus disease-19; Novel coronavirus pneumonia; Hydroxychloroquine; Treatment outcome; Safety

December 2019, the Wuhan City, Hubei Province has been found in many cases of pneumonia of unknown causes, and quickly spread [1] . 2020 January 31, WHO will this outbreak as a public health emergency of international concern [2] . Gene sequence analysis showed that this epidemic pathogens β is a coronavirus, severe acute respiratory syndrome (severe acute respiratory syndrome, SARS) virus is highly homologous to the International Committee on Taxonomy of Viruses will be named severe acute respiratory syndrome coronavirus virus 2 (severe acute respiratory syndrome coronavirus 2 , SARS-CoV-2), WHO will be caused by infections officially named 2019 Coronavirus disease (corona virus disease-19 , COVID-19) [3] . SARS-CoV-2 with a strong infectious, there is no specific anti-viral drugs or vaccines are coronavirus [4] .

Chloroquine is a widely used anti-malarial drugs, and autoimmune diseases, both broad-spectrum antiviral activity. Chloroquine endosomal pH values the change, depends on the inhibition of viral replication step and pH exert a direct antiviral effect. Have a role in the inhibition of the dengue virus, Zika virus and HIV and other viral replication [5-6] . In 2005, Vincent et al [7] Found chloroquine can effectively block the SARS-CoV infection in cell lines. National health committee "novel coronavirus pneumonia treatment program (Trial Sixth Edition)" (hereinafter referred to as "treatment program") is recommended for chloroquine phosphate COVID-19 Patients with antiviral therapy [8] . Hydroxychloroquine sulfate of 4-aminoquinoline antimalarials derivatives, addition of a hydroxyl group on the basis of more chloroquine,

The efficacy is quite low toxicity. As a traditional "old drug", hydroxychloroquine sulfate and higher security it is to therefore COVID-19

One of the drugs with potential efficacy. This study was a single-center, prospective, randomized and open-label study designed to explore the next step to carry out hydroxychloroquine sulfate treatment COVID-19 The efficacy and safety studies provide data base.

1 Subjects and methods

1.1 Object

Collect 30 cases in Shanghai Public Health Clinical Center hospitalization 2020 February 6 to 25 COVID-19

Diagnosed patients. Inclusion criteria: Age ≥18 years, according to "treatment program" confirmed COVID-19 And signed informed consent. Exclusion criteria: ① to chloroquine, patients hydroxychloroquine allergies; ② pregnant women; ③ combined with cardiac, lung, kidney, brain, blood and other vital organs serious diseases in patients with dysfunction with; ④ retinal disease, hearing loss or hearing loss patients; ⑤ patients with severe neurological or psychiatric illness; ⑥ researchers believe can not be required to complete the study or inappropriate research participants.

1.2 Grouping and treatment

Subject 1: 1 ratio were randomly assigned to the test group and control group. Experimental group received conventional therapy oral hydroxychloroquine sulfate 400 mg, 1 times / d, treatment for 5 d; control group received conventional treatment, including bed rest, oxygen, symptomatic and supportive therapy, the use of "treatment program" recommended anti viral drugs such as interferon α atomizing, orally lopinavir / ritonavir (Kaletra) or the like, if necessary, administration of antibacterial drugs. All subjects were screened on the day of admission, complete randomization and initiation of treatment (including antiretroviral therapy). Demographic data sets at the time of enrollment, clinical manifestations, laboratory results and chest CT findings were not significantly different (Table 1). All patients received interferon α spray treatment, while the test group 12 (80.0%) Patients received treatment Abidor; control group 10 example(66.7%) Accepts Abidor treatment,

2 example(13.3%) Receiving lopinavir / ritonavir therapy.

This study by the Shanghai Public Health Clinical Center ethics committee approval and registration (NCT04261517).

table 1 Science and clinical characteristics of the two groups compare population

Table 1 Demographic data and clinical characteristics of the two groups

[$\bar{sx}$ • or $M(Q_1, Q_3)$or n (%)]

Group	*n* male*	The average age of the average duration (d)	heat	Basic illness*		
				Diabetes, high blood pressure		Chronic obstructive pulmonary disease
test group 159 (60.0)	50.5 ± 3.8	6.6 ± 3.9	9 (60.0) 5 (33.3) 1 (6.7)			0 (0.0)
The control group 1512 (80.0) 46.7 ± 3.6		5.9 ± 4.1	13 (86.7) 3 (20.0) 1 (6.7)			1 (6.7)
t / *U* value - -	0.72	0.45	-	-	-	-
P value - > 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Group	*n* White blood cell count (× 10⁹/ L)	Lymphocyte counts (× 10⁹/ L)	ALT (U / L)	eGFR (mL · min⁻¹ · 1.73m⁻²)	Lactate (Mmol / L)	CD4 + Cell count (cells / μL)	chest CT Lesion (lungs / one lung) *
test group 15 5.2 (3.9 - 6.7)	1.11 ± 0.43	18 (15 to 23)	117 ± 29	1.4 ± 0.4	415 (275 to 589)	12/3	
The control group 15 4.9 (4.5 - 7.4)	1.18 ± 0.55	24 (14 to 47)	120 ± 29	1.4 ± 0.5	395 (272 - 710)	14/1	
t / *U* value --101	0.39	87	0.30	0.19	110	-	
P value - > 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	

"-" No data. * Fisher test. ALT : Alanine aminotransferase; eGFR : Glomerular filtration rate valuation.

1.3 clinical data collection and follow-up

When the group of subjects history taking, physical examination, laboratory tests and epidemiological characteristics collection. Clinical classification of the subject with reference to "treatment program" implementation. The first group of the day 0,3,5,7 subjects of vital signs, clinical symptoms, laboratory test results and adverse events were recorded. The study followed up for 2 weeks.

1.4 study endpoint

The primary endpoint was the seventh day swabs, sputum or lower respiratory tract secretions virological clearance or patients died within 2 weeks; secondary end points were 2 weeks of serious adverse drug events occur or subject transfer condition as severe and critical type. Respiratory specimens SARS-CoV-2 In the nucleic acid detection and the last detection result based on the time, such as detection of viral nucleic two consecutive negative, clearance time nucleic acid detection using the first time.

1.5 Statistical Methods

use STATA 13.0 Software for statistical analysis. Normally distributed measurement data with the mean ± Standard deviation ($\bar{x} \pm s$) Describes, does not conform to the normal distribution of measurement data with the median (upper and lower quartile) [$M(Q_1, Q_3)$] Describe count data by the number of cases and the percentage [$n(\%)$] description. Measurement data between groups were compared using t Test (normal distribution) or rank sum test (non-normal), groups were compared using count data χ^2 Inspection or Fisher test. $P < 0.05$ There is a statistically significant difference.

2 Results

2.1 Test group and control group the efficacy of

During treatment, the test group 1 Patients develop severe, and at the 4 Day disabled test drug. For the intent analysis, after the group 7 Days, the experimental group 13 example(86.7%) And control group 14 example(93.3%) In patients with throat swab virus nucleic acid test is negative ($P > 0.05$). in 2 Visit week period, all subjects throat viral nucleic acid detection are converted to negative, wherein negative test group throat viral nucleic acid for the first time after admission 4 (1 to 9) Days of the control group 2 (1-4) Days, no statistically significant difference ($U = 83.5$, $P > 0.05$). The first test group after admission 1 (0-2) Day temperature returned to normal, the control group after admission 1 (0-3) Day temperature returned to normal. On the imaging findings, the test group 5 example(33.3%) And control group
7 example(46.7%) Were enrolled 3 d After a review of progress emerged, all patients in the subsequent review of the lesions were prompted improved. To the end of the follow-up period, all subjects were alive.

2.2 The test group and control group of adverse reaction compared to the situation

The control group did not appear obvious symptoms of new hair, but there are 3 Times of adverse events, including 1 example(20%) Has a transient anemia and elevated aspartate aminotransferase, 1 Patients had elevated serum creatinine; Test group 4 Times of adverse events, including 2 Cases of diarrhea, 1 Cases of severe fatigue and development, 1 Patients had a transient elevated aspartate aminotransferase. Consider occur regardless of which treatment subjects in the test group for the development of severe adverse events. After all adverse events after discontinuation disappeared or symptomatic treatment, patients in the development of severe give high flow nasal cannula oxygen therapy and other treatment of the condition also improved. Between the two groups was not statistically significant difference in the incidence of adverse events ($P > 0.05$).

3 Discussion

"Treatment plan" as recommended chloroquine phosphate COVID-19 One program antiviral treatment. Up 2020 year 2 month 25 Japan, the Chinese Clinical Trial Register (http:. // www chictr.org.cn/) Registration by chloroquine treatment COVID-19 The various research has been up to twenty one Item, most studies employed chloroquine phosphate (500 mg , 2 Times / d , For taking 10 d) Or hydroxychloroquine sulfate (400 mg , 1 Times / d , For taking 10 ~ 14 d) [9] .

80% of COVID-19 Patients for light or ordinary type. This data type are common in all patients showed a standard dose of hydroxychloroquine sulfate (400 mg , 1 Times / d) Did not show clinical treatment has the effect of improving the patient's symptoms, and the like to accelerate virological suppression. It is noteworthy that, after the enrollment information in this article in the vast majority of patients 1 (0-3) d Body temperature returned to normal, 2 (1-4) d Throat viral nucleic acid can not be detected i.e., the center of which the present 2020 year 1 month 20 To 2 month 6 The results day cases were significantly different. 2020 year 1 month 20 To 2 month 6 Patients enrolled in day 4 d

After body temperature returned to normal, negative throat swab virus nucleic acid median time about admission 7 day[10] . This may suggest over time due to changes in the epidemiological factors, temperature, humidity, and may change the virulence of the virus, COVID-19 There may reduce the severity of the trend. In this treatment group had relatively good, the general type COVID-19

Patients looking for better efficacy of the drug will encounter a "ceiling effect." Using the results of the test were calculated, hydroxychloroquine sulfate To obtain better efficacy than the control group or inferiority conclusion, at least 784 Subjects. If the subject off, excluding other factors to consider, the number of cases to be nearly 900 example. This is a huge challenge for the current clinical study for. Therefore, to find a more appropriate population for evaluation endpoint or hydroxychloroquine sulfate (in fact, all other drugs) effect of treatment may be more feasible clinically as severe assess whether or critically ill patients may reduce mortality rate. In addition, if, over time, gradually reduce the subject's condition indeed, even more it reminds us the importance of clinical research conduct random controls. If carried out single-arm study, and historical data as a control, you may get a false positive result (ie, certain drugs found effective) [11] .

In summary, this study suggests that the current common type COVID-19 Overall better patient outcomes, study virus negative rate, aggravation rate of the primary endpoint is difficult to effect treatment regimen is determined. Follow-up studies need to identify more appropriate to carry out the crowd and endpoints, sample size, etc. and give full consideration to the feasibility test.

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