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Coronavirus Pandemic

Existing drug treatments cannot significantly shorten the clinical cure time of children with COVID-19

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Abstract

Introduction: COVID-19 has become a global health security issue, it has caused more than half a million deaths worldwide so far, the treatment strategies are the most concerned issues for clinicians. In this study, the treatments and outcomes in 40 pediatric patients diagnosed with COVID-19 and treated with different drugs were evaluated.

Methodology: All cases were diagnosed with COVID-19 nucleic acid positive by using RT-PCR or clinical manifestations, imaging specific characteristics and epidemiological clinical diagnosis. The biological information and first symptom of all cases were collect. A variety of treatments were employed and the outcomes were evaluated by Cox regression analysis. Multivariable analysis was performed to evaluate cure rate at 14 days with different drug treatment.

Results: The average length of hospital stay was 10.4 days. The cure rate was increased with the treatment time extended and 90% of pediatric patients were cured and discharged after 14 days' treatment. And multivariable analysis results proved that none of the covariates were related to the cure rate at 14 days with different drug treatment since *p* values were over 0.05.

Conclusions: Multivariable analysis suggested that the present drug treatments cannot significantly shorten the clinical cure time and improve the cure rate of children with COVID-19.

Key words: Coronavirus disease 2019; pediatric patients; different treatment agents; cure rate.

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Introduction

Since December 2019, a number of patients infected by the coronavirus disease 2019 (COVID-19) have been detected in Wuhan City, capital of Hubei province, as the center. As of 19 February 2020, there has been more than 74,000 confirmed cases on the Chinese mainland, resulting in 2,118 deaths [1] - nearly three times the reported number of deaths during the SARS outbreak world-wide in 2003 [2]. Moreover, there are no proven and specific antiviral drugs or vaccines for COVID-19 although there are agents that were used during the SARS and MERS [3,4], so the treatment strategies are the most concerned issues for clinicians.

The early reported patients were elderly and those with underlying chronic diseases, by the ongoing outbreak driven by the COVID-19, the number of children infected gradually increased, spreaing to premature babies, infants and young children. Although a few numbers of drugs have been shown to be effective in the treatment of adult patients with COVID-19, and there are gradually mature guidelines for the treatment of adults, there is a lack of evaluation and reports on the clinical efficacy of drugs in children. In this study, we retrospectively analyzed the treatment and outcome of pediatric cases in Wuhan Children's Hospital, which is the only designated hospital for pediatric diagnosed with COVID-19 in Hubei Province.

Methodology

40 pediatric patients (18 years of age or younger) who were diagnosed with COVID-19 and treated in Wuhan Children's Hospital between 20 January and 20 February 2020 were involved in this study. The studies involving human participants were reviewed and approved by the Ethics Committee of Wuhan Children's hospital.

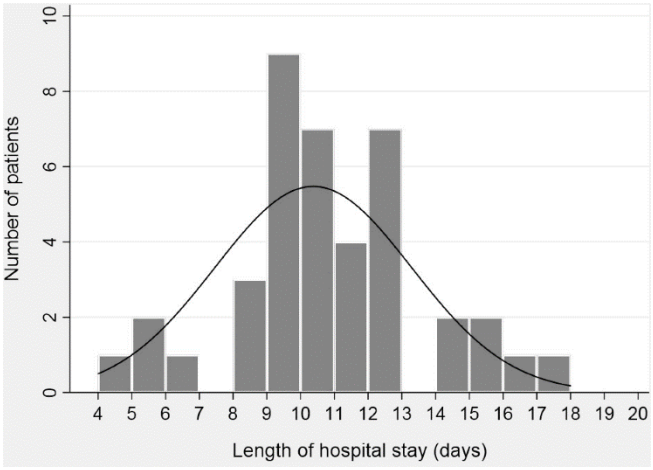
All cases were diagnosed with COVID-19 nucleic acid positive by using RT-PCR or clinical manifestations, imaging specific characteristics and

epidemiological clinical diagnosis. Demographic, laboratory, clinical data and other information of the patients were all collected. The treatments with different drugs were recorded. The average durations of (i) temperature return to normal, (ii) pulmonary CT improvement and (iii) COVID-19 RNA clearance (the time from the first time PCR test positive for COVID-19 nucleic acid to the negative result without a positive test afterward) were all calculated, as well as the length of hospital stay. Patients could be discharged if their PCR results were negative for at least two consecutive times and the CT results improved significantly with clinical symptoms obviously improved. In addition, the cure rates at 7, 10 and 14 days were obtained respectively. The treatment and outcome of all cases were analyzed. Multivariable analysis was performed using the Cox regression analysis to evaluate cure rate at 14 days with different drug treatment.

Table 1. The characteristics of pediatric patients with COVID-19 (n = 40).

Biological information	**Mean ± SD (Range)**
Age (years)	5.61 ± 4.63 (0.21-16.75)
Height (cm)	111.95 ± 38.44 (56-165)
Weight (kg)	24.85 ± 20,93 (4.5-80)
BMI	17.75 ± 3.66 (14.11-31.59)
Gender: Male/Female	21/19
First symptom	**Number (percent)**
Fever	35 (87.5%)
Dry cough	25 (62.5%)
Abnormal value of C-reactive protein	22 (55.0%)
Treatments	**Number (percent)**
Interferon	40 (100.0%)
Budesonide	36 (90.0%)
Abidol (oral)	2 (5.0%)
Oseltamivir (oral)	5 (12.5%)
Ribavirin (Intravenous drip)	3 (7.5%)
Cephalosporin (Intravenous drip)	28 (70.0%)
Azithromycin (oral)	9 (22.5%)
Traditional Chinese medicine (oral)	10 (25.0%)
Gamma globulin (Intravenous drip)	3 (7.5%)
Outcomes	**Mean ± SD (Range)**
Duration of temperature return to normal (day)	2.95 ± 2.09 (1-8)
Duration of pulmonary CT improvement (day)	10.30 ± 2.08 (7-17)
Duration of COVID-19 RNA clearance (day)	6.41 ± 2.90 (4-18)
Length of hospital stay (day)	10.38 ± 2.91 (1-12)
Number of cured patients at 7 days	4 (10.0%)
Number of cured patients at 10 days	23 (57.5%)
Number of cured patients at 14 days	36 (90.0%)

Figure 1. Length of patients' stay in hospital.



Results

Demographic and clinical characteristics

There were in total 40 children patients diagnosed with COVID-19 involved in this study, including 21 males (52.5%) and 19 females (47.5%) with the average age of 5.6 years (range from 0.21 to 16.75 years). 30 patients were diagnosed with COVID-19 directly according to the throat swab samples tested positive for COVID-19 nucleic acid. The other 10 patients were diagnosed according to imaging examination combined with clinical manifestations and epidemiological diagnosis (their close touching relatives were diagnosed with COVID-19 by PCR nearly one week after admission) because of the false negative results of PCR. The first clinical symptoms of most of the patients were fever (87.5%) and dry cough (62.5%). Twenty-two patients (55%) presented abnormal value of C-reactive protein. All patients were classified as mild pneumonia in accordance with the Child Care Guidelines.

Treatments

The treatments employed were listed in Table 1. All cases received interferon-α nebulization and thirty six patients (90%) were co-administrated budesonide to relieve inflammatory response of lung airway. Twenty eight patients (70%) received cephalosporin treatment to prevent secondary bacterial infection. Ten patients (25%) were given traditional Chinese medicine for antiviral treatment. Nine patients (22.5%) with Mycoplasma pneumonia infection were orally administrated azithromycin. Ten patients were treated with antivirals including abidol (5.0%), oseltamivir

(12.5%) and ribavirin (7.5%). Only three patients (7.5%) received gamma globulin as an immune supportive treatment.

Clinical outcomes

Clinical outcomes were showed in Table 1. As can be seen, the average length of hospital stay was about 10.4 days. The average durations of temperature return to normal, pulmonary CT improvement and COVID-19 RNA clearance were 3.0, 10.3 and 6.4 days respectively. Figure 1 showed the histogram of the length of patients stay in hospital. In addition, the number of cured patients at 7, 10, and 14 days were also analyzed and the results were showed in Table 1. The results suggested that 90% of pediatric patients were cured and discharged after 14 days' treatment. As shown in Table 2, multivariable analysis was performed to evaluate cure rate at 14 days with different drug treatment. The results proved that none of the covariates were related to the cure rate at 14 days with different drug treatment since P values were over 0.05, which suggested the present treatments had no significant impact on the cure rate at 14 days.

Discussion

People of all ages are susceptible to COVID-19. Comparing with adults, the incidence of COVID-19 in children is significantly lower and most pediatraric cases were mild, and no death case has been reported to date. Children have fewer opportunities to enter crowded places, which can be potential factors for the relatively low incidence. Besides, referring to the lower incidence of SARS in children in 2003 compared to adults, we find that children may be less susceptible to viruses based on their cellular structure or immunity [5].

Children with COVID-19 at the early stage mainly manifested as fever, fatigue, cough, and may be accompanied by nasal congestion, runny nose, sputum, headache, etc.[6], and the symptoms usually disappear within one week under intervention. Our research found that children are usually discharged within two weeks, the mean number of hospitalizations is 10.38 days. In addition, the cure rates at 7, 10, and 14 days were 10%, 57.5% and 90%, respectively. In adults, the apparent stage of symptoms is 1 to 2 weeks after the first symptoms, and the duration time is 3 to 4 weeks or longer [5].

There are no established guidelines for the diagnosis and treatment of COVID-19 in children. The treatment plan is improved based on the adult treatment experience. In the clinical treatment of our pediatric cases, all cases received interferon-α nebulization, three patients (7.5%) were co-administrated ribavirin and thirty six patients (90%) were co-administrated budesonide to relieve inflammatory response of lung airway. For mild cases, interferon-α can reduce viral load in the early stage of infection which can help to alleviate symptoms and shorten the course of disease [7]. However, all of the patients in our study were given interferon-α, the clinical effect was difficult to evaluate. But our analyses showed that the treatment of interferon-α co-administrated with other drugs had no significant impact on the cure rate. *Omrani AS etc.* had found ribavirin and rIFN-α2a therapy is associated with significantly improved survival at 14 days, but not at 28 days in patients with severe MERS-CoV infection [8]. However, a multicenter retrospective study involving 349 patients led by *Arabi YM etc.* reached a different conclusion, ribavirin/rIFN (ribavirin and/or rIFN-α2a, rIFN-α2b, or rIFN-β1a) therapy was commonly used in critically ill MERS patients but was not associated with reduction in 90-day mortality or in faster MERS-CoV

Table 2. Multivariate analysis of cure rate at 14 days.

Covariates	Hazards Ratio	95%CI	P-value
Biological baseline			
Age	0.991	0.896-1.097	0.866
BMI	0.962	0.833-1.109	0.591
Drugs			
Interferon	1.000	——	——
Budesonide	0.367	0.057-2.351	0.290
Abidol	0.489	0.053-4.480	0.527
Oseltamivir	0.363	0.055-2.387	0.292
Ribavirin	0.473	0.070-3.223	0.445
Cephalosporin	0.807	0.319-2.041	0.651
Azithromycin	0.610	0.223-1.669	0.336
Traditional Chinese medicine	1.038	0.407-2.646	0.938
Gamma globulin	0.822	0.058-11.563	0.884

RNA clearance [9]. Although ribavirin and type I IFN showed inhibition of SARS-CoV in tissue culture in vitro studies [10], the clinical efficacy of ribavirin and interferon for SARS is controversial. A systematic review in 2006 described that αIFN did not significantly improve the prognosis of SARS patients, meanwhile ribavirin increased the incidence of complications such as anemia and liver damage [10]. Thirty six patients were treated with budesonide inhalation. *Jian Guo Hong etc*. has found nebulized budesonide, the agent of focus in all trials analyzed, significantly reduced the risk of further asthma exacerbations compared with placebo, cromolyn sodium, and montelukast. Nebulized corticosteroids (NebCS) are effective and well tolerated in patients 5 years of age or younger for the management of acute and chronic asthma [11]. Whereas, our data displayed that nebulized budesonide has no significant effect on the treatment of COVID-19 in children. Oseltamivir, a commonly used antiviral drug which is a neuraminidase inhibitor, has already been confirmed that it has no effect on COVID-19 because coronaviruses do not produce neuraminidase [12]. The chemical structure of abidol is similar to oseltamivir. Abidol is mainly used to prevent and treat influenza A and B viruses. Based on preliminary in vitro cell experiments, Li Lanjuan's team believes that Abidol and Darunavir can effectively inhibit COVID-19. Still, the dose, effectiveness and safety for children have not yet been explored. And another study shows that Abidol has not been found to improve symptoms or shorten the time of viral nucleic acid transition in respiratory specimens, and their effectiveness remains to be confirmed by further clinical studies [13], the result of this study is also consistent with ours. Traditional Chinese Medicine have been proposed against COVID-19 in ten cases, Whereas, no significant clinical effect was found in our study and its efficiency and safety in children remain to be verified.

For the moment, the dates of pediatric cases are still limited. And our analyses suggested that the current drug treatments cannot significantly shorten the clinical cure time of children with COVID-19. To look into more effective treatment strategies is a significant issue for us and the outcome of the pediatric patients' therapy on COVID-19 needs to be evaluated in a larger sample.

The limitations of our work are as follows: (i) Due to the limited cases of children patients diagnosed with COVID-19 in Wuhan, no bigger sample size could be included in our study; (ii) Our research is a retrospective study and no parallel control group is included.

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Authors' Contributions

Liuliu Gao, Mengting Li and Yang Wang performed the major research. The manuscript was written mainly with the efforts of Liuliu Gao and Mengting Li. Yang Wang, Qi Ye, Jun Wan and Sichan Li provided the statistical analysis. Hua Xu, Liang Shi, Yan Mei and Changlin Liu have given approval to the final version of the manuscript.

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