

**The value of high-flow nasal cannula oxygen therapy in treating patients with severe novel coronavirus pneumonia**

**Running Title:** Treatment patients with severe COVID-19

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## **Abstract**

**Objective:** This study aimed to investigate the value of high-flow nasal cannula (HFNC) oxygen therapy in treating patients with severe novel coronavirus pneumonia (COVID-19). **Methods:** The clinical data of 22 patients with severe COVID-19 were collected. The heart rate (HR), respiratory rate (RR) and oxygenation index ( $PO_2/FiO_2$ ) at 0, 6, 24 and 72 hours after treatment were compared between the HFNC oxygen therapy group and the conventional oxygen therapy (COT) group. In addition, the white blood cell (WBC) count, lymphocyte (L) count, C-reactive protein (CRP) and procalcitonin (PCT) were compared before and at 72 hours after oxygen therapy treatment. **Results:** Of the included patients, 12 were assigned to the HFNC oxygen therapy group and 10 were assigned to the COT group. The differences in HR, RR,  $PaO_2/FiO_2$ , WBC, L, CRP and PCT at 0 hours between the two groups were not statistically significant. At 6 hours after treatment with the two oxygen therapies, HR, RR and  $PaO_2/FiO_2$  were better in the HFNC oxygen therapy group than in the COT group ( $p < 0.05$ ), while at 24 and 72 hours after treatment with the two oxygen therapies,  $PaO_2/FiO_2$  was better in the HFNC oxygen therapy group than in the COT group ( $p < 0.05$ ), but the differences in HR and RR were not statistically significant. At 72 hours after treatment, L and CRP had significantly improved in the HFNC

oxygen therapy group compared with the COT group, but the differences in WBC and PCT were not statistically significant. The length of stay in the intensive care unit (ICU) and the total length of hospitalization were shorter in the HFNC oxygen therapy group than in the COT group, and the differences between the two groups were statistically significant. **Conclusion:** Compared with COT, early application of HFNC oxygen therapy in patients with severe COVID-19 can significantly improve oxygenation and RR, and HFNC oxygen therapy can improve the infection indexes of patients and reduce the length of stay in the ICU of patients. Therefore, it has high clinical application value.

**Keywords:** pneumonia; Coronavirus disease 2019; high nasal flow oxygen therapy

## **Introduction**

Since December 2019, patients with pneumonia of unknown origin have been admitted to many hospitals in Wuhan. The main symptoms of the patients were fever and fatigue, and a few patients had dyspnea. The related virus was tested and typed by experts, and novel coronavirus was detected in the laboratory on January 7, 2020. The World Health Organization named this virus novel coronavirus 2019 (COVID-19). The pneumonia caused by this virus is different to community-acquired pneumonia (CAP) and hospital-acquired pneumonia/ventilator-acquired pneumonia, as it has

strong ability to spread from person to person. The COVID-19 Diagnosis and Treatment Plan (trial version 7) [1] states that patients with asymptomatic infection can also be a source of infection. COVID-19 has been included in class B infectious diseases stipulated in the Law of the People's Republic of China on the Prevention and Control of Infectious Diseases and is managed in the same way as class A infectious diseases. Furthermore, according to the severity of patients' condition, COVID-19 was classified as mild, moderate, severe and critical. Patients with the severe type of the virus often have varying degrees of hypoxia and dyspnea, and therefore respiratory support therapy is very important for these patients. High-flow nasal cannula (HFNC) oxygen therapy is a new respiratory support technology that has attracted attention in medical applications in recent years,. It has the advantages of stable oxygen supply performance and constant oxygen output concentration. Moreover, it can maintain the air temperature in the range of 31–37°C and provide gas humidity of up to 100%. Therefore, the technology has the advantages of the common nasal tampon and mask. The positive end-expiratory pressure (PEEP) it produces can increase the functional residual capacity and bring about almost the same partial function as noninvasive ventilation. Compared with the traditional oxygen therapy, it has the advantages of high comfort, good compliance, and an obvious therapeutic effect. Many studies have proved its application value in the treatment of acute respiratory failure [2,3]. Therefore, the application of HFNC oxygen therapy may improve the prognosis of patients with COVID-19. This study was designed to investigate the value of HFNC oxygen therapy in treating patients with severe

COVID-19. The study results are reported below.

## **1. Data and Methods**

### **1.1 Subjects**

The data of 22 patients diagnosed with severe COVID-19 in Fuyang Second People's Hospital between January 2020 and February 2020 were collected. Of these patients, 12 were assigned to the HFNC oxygen therapy group and 10 were assigned to the conventional oxygen therapy (COT) group. Inclusion criteria: The age of the patients was >18 years; the patients met the diagnostic criteria for patients with severe COVID-19 in the COVID-19 Diagnosis and Treatment Plan (trial version 7) [1]. Exclusion criteria: Partial pressure of carbon dioxide ( $\text{PaCO}_2$ ) >50 mmhg or previous chronic obstructive pulmonary disease or asthma; acute cardiogenic pulmonary edema or acute coronary syndrome; Glasgow coma scale <13. Elimination criteria: During the treatment, the patient could not cooperate with and tolerate HFNC oxygen therapy; pneumothorax occurred during the treatment; the patient needed invasive mechanical ventilation during the treatment; the patient could not continue the treatment due to their deterioration during the course of treatment; the patient was unable to participate in the whole trial. In this study, all patients expressed their willingness to participate in the trial and provided a signed form giving informed consent.

### **1.2 Research methods**

#### **1.2.1 HFNC oxygen therapy group**

After being diagnosed with severe COVID-19 by the COVID-19 treatment expert group of Fuyang Second People's Hospital, the patients were immediately admitted to the intensive care unit (ICU), and HFNC oxygen therapy was applied. The HFNC oxygen therapy machine model was Optiflow PT101AZ (Fisher & Paykel, Auckland, New Zealand). The initial parameters were as follows: temperature was 37°C, flow rate was 50 L/min, and oxygen concentration was 50%. Parameters were adjusted according to blood oxygen saturation level ( $SpO_2$ ), blood gas and tolerance, maintaining  $SpO_2$  above 93%. The duration of continuous treatment for all patients was more than 72 hours.

### **1.2.2 COT group**

After being diagnosed with COVID-19 by the treatment expert group and admitted to the ICU, the patients began to inhale oxygen utilizing a nasal catheter or a common mask (including Venturi and oxygen storage mask). The initial oxygen absorption flow was set at 5 L/min, which was adjusted according to the condition of  $SPO_2$ , maintaining  $SpO_2$  above 93%. The duration of treatment was more than 72 hours.

### **1.2.3 Data collection**

One mL of blood was drawn from the radial artery of the patient and analyzed using the Philips blood gas analyzer (RAPIDPOINT 500, Siemens Healthcare Diagnostics Inc. 511 Benedict Avenue, Tarrytown, New York 10591 USA). The heart rate (HR), respiratory rate (RR) and oxygenation index ( $PaO_2/FiO_2$ ) values of all patients were collected at 0, 6, 24 and 72 hours after treatment. Furthermore, 5 mL of fasting venous

blood was drawn 1 day before and 3 days after HFNC oxygen therapy and COT application, centrifuged, and tested for white blood cell (WBC) count, lymphocyte (L) count, C-reactive protein (CRP) and procalcitonin (PCT) by a blood routine analyzer(Sysmex XE2100,Sysmex,Kobe, Japan) and automatic biochemical analyzer (Hitachi 7600-020,HITACHI,No. 6-6, Yitinu, Marunouchi, Chiyoda District, Tokyo). In addition to oxygen therapy, all patients were given lopinavir/ritonavir tablets and interferon  $\alpha$  as antiviral treatment for regulation of gastrointestinal flora and protection of organ function, and their vital signs and other symptoms were monitored.

### **1.3 Statistical analysis**

Statistical analysis was conducted using SPSS16.0 (SPSS Inc Chicago,USA) statistical software. Measurement data were expressed as mean  $\pm$  standard deviation ( $\bar{x} \pm SD$ ) and compared utilizing a t-test or repeated measures analysis of variance (ANOVA). Count data were expressed as frequency or percentage and compared utilizing a Chi-square test.  $P < 0.05$  was considered statistically significant.

## **2. Results**

### **2.1 Comparison of general information**

The differences in age, gender, interval from onset to diagnosis and underlying diseases (hypertension, diabetes, coronary heart disease) between the two groups were not statistically significant ( $p > 0.05$ ), as shown in Table 1.

## **2.2 Comparison of HR, RR and PaO<sub>2</sub>/FiO<sub>2</sub> at each time point between the two groups**

The differences in HR, RR and PaO<sub>2</sub>/FiO<sub>2</sub> at 0 hours of treatment with the two oxygen therapies between the two groups were not statistically significant. At 6 hours after treatment with the two oxygen therapies, HR, RR and PaO<sub>2</sub>/FiO<sub>2</sub> were better in the HFNC oxygen therapy group than in the COT group ( $p < 0.05$ ). At 24 and 72 hours after treatment, PaO<sub>2</sub>/FiO<sub>2</sub> was better in the HFNC oxygen therapy group than in the COT group ( $p < 0.05$ ), but the differences in HR and RR were not statistically significant ( $p > 0.05$ ). Repeated measures ANOVA revealed that the differences in HR, RR and PaO<sub>2</sub>/FiO<sub>2</sub> at different time points were statistically significant ( $F = 3774.719, 4484.716, 2399.247$ , respectively,  $p = 0.000$  for all), and the difference in the improvement of PaO<sub>2</sub>/FiO<sub>2</sub> between the two groups was statistically significant ( $F = 6.201, p = 0.022$ ), but the differences in the improvement of HR and RR were not statistically significant ( $p > 0.05$ ), as shown in Tables 2, 3 and 4, respectively. At 6, 24 and 72 hours after treatment, RR was lower in the HFNC oxygen therapy group than in the COT group, and PaO<sub>2</sub>/FiO<sub>2</sub> was higher in the HFNC oxygen therapy group than in the COT group, as shown in Figures 1 and 2, respectively.

## **2.3 Comparison of infection indexes between two groups before and after oxygen therapy**

The differences in CRP, PCT, WBC and L before HFNC oxygen therapy and COT treatment between the two groups were not statistically significant ( $p > 0.05$ ). At 72



hours after treatment, CRP and L in the HFNC oxygen therapy group had improved significantly, the differences between the two groups were statistically significant ( $p < 0.05$  for all), but the differences in PCT and WBC were not statistically significant ( $p > 0.05$  for all), as shown in Table 5.

#### **2.4 Comparison of length of ICU stay and total length of hospitalization between the two groups**

All patients in this study were cured and discharged. The length of ICU stay was  $4.00 \pm 0.74$  days in the HFNC oxygen therapy group and  $4.90 \pm 1.00$  days in the COT group, and the difference was statistically significant ( $p = 0.024$ ). The total length of hospitalization was  $14.67 \pm 1.97$  days in the HFNC oxygen therapy group and  $16.60 \pm 2.54$  days in the COT group, but the difference was not statistically significant ( $p = 0.058$ ), as shown in Table 6.

### **3. Discussion**

COVID-19 is a newly emerging infectious respiratory disease. This virus is the third type of coronavirus that we have found and identified, as severe acute respiratory system coronavirus (SARS-CoV) was found in China in 2003 and Middle East respiratory system coronavirus (MERS-CoV) was found in the Middle East in 2012. The epidemic situation in China has been controlled, whereas the epidemic situation in other countries around the world is gradually increasing. Because of its accumulated experience in the early anti epidemic process, China has contributed

much campaign experience and many campaign teams of experts to the world. Based on the previous understanding of SARS, Chinese scholars found that COVID-19 causes a series of respiratory symptoms similar to SARS, but it seems to be more powerful in dissemination than SARS; consequently, some patients need to be treated in the ICU [4]. As HFNC oxygen therapy is a new oxygen therapy strategy that was developed in recent years, it was not applied to SARS in 2003. On May 28, 2015, Huizhou City, Guangdong Province, China received the first imported case. In this case, HFNC oxygen therapy was applied during hospitalization. After application of HFNC oxygen therapy, the respiratory and circulatory function of the patient improved significantly, and finally, patients were cured and discharged [5].

In this study, observation of the indexes of circulatory respiration at different time points in patients with severe COVID-19 after applying different oxygen therapy strategies revealed that compared with the COT group, in the HFNC oxygen therapy group, HR and RR had improved more significantly at 6 hours after treatment, but the differences in HR and RR at 24 and 72 hours after treatment between the two groups were not statistically significant. Moreover, the  $\text{PaO}_2/\text{FiO}_2$  of the HFNC oxygen therapy group was better than that of the COT group, and the difference was statistically significant. In addition, the RR of the HFNC oxygen therapy group was lower than that of the COT group, and the  $\text{PaO}_2/\text{FiO}_2$  of the HFNC oxygen therapy group was higher than that of the COT group. This is consistent with the results of many foreign studies [6,7,8], all of which proved that compared with conventional oxygen therapy, HFNC oxygen therapy is more effective in improving the RR and

PaO<sub>2</sub>/FiO<sub>2</sub> of patients with acute respiratory failure. By analyzing the clinical effect of HFNC oxygen therapy in the treatment of acute hypoxic respiratory failure, Chinese scholars Wang et al. [9] found that after HFNC oxygen therapy treatment, RR and PaO<sub>2</sub>/FiO<sub>2</sub> had improved significantly, and the improvement in RR and PaO<sub>2</sub>/FiO<sub>2</sub> was more obvious with the prolongation of the treatment time.

The reason for this result is related to the characteristics of HFNC oxygen therapy that are outlined below. Compared with ordinary oxygen therapy devices (nasal catheter, mask), HFNC oxygen therapy has a unique air-oxygen mixing device. This device can mix air and oxygen and output constant gas flow and oxygen concentration, which is not affected by other external factors. In addition, the humidification device and heating pipeline of HFNC oxygen therapy can accurately heat and humidify the gas to the appropriate level for patients, reduces the loss of heat and water in the respiratory tract, and is conducive to the recovery of airway ciliary function, thus promoting the discharge of secretions [10]. Moreover, HFNC oxygen therapy can provide gas flow of up to 60 L/min, which can produce a certain PEEP effect. Furthermore, with the increase in the gas flow rate, PEEP will also increase. A study revealed that for every 10 L/min increase in the gas flow rate, PEEP increased by 0.5–1.0 cm H<sub>2</sub>O, and the flow rate of 60 L/min could produce 8.7 cm H<sub>2</sub>O of PEEP in the pharyngeal cavity of female patients [11]. This effect could promote the re-expansion of alveoli, increase functional residual capacity, and reduce the respiratory work [12]. In addition, since HFNC oxygen therapy has a high gas flow rate, it has a certain effect of respiratory tract flushing. When the exhaled air containing a low concentration of oxygen in the

dead cavity of the nasopharynx anatomy is washed out of the body, the patient will inhale fresh higher concentration oxygen, thereby improving the oxygenation [13,14,15].

Some of the patients with COVID-19 had bacterial infection. The COVID-19 Diagnosis and Treatment Plan (trial version 7) [1] states that in the early stage of the virus, the patient's WBC count is normal or decreased, the L count may reduce in the majority of patients, CRP and erythrocyte sedimentation rate increase, and PCT is usually normal. Furthermore, the guidelines state that a progressive decrease in the L count and a progressive increase in CRP are the clinical early warning indexes of severe and critical types of COVID-19. In this study, the data of 22 patients with severe COVID-19 were statistically analyzed. Results revealed that in the early stage, L count decreased, CRP increased, and WBC and PCT were within the normal range, which is the same as described in the guidelines. After 72 hours of HFNC oxygen therapy or COT treatment, the above infection indexes were analyzed again. CRP and L had improved in both groups, but in the HFNC oxygen therapy group they had improved more significantly. Therefore, HFNC oxygen therapy may be able to help accelerate the recovery of patients with severe COVID-19. Cuq et al. [16] studied the heating and humidification functions of HFNC oxygen therapy and found that after inhaling the air with a suitable temperature and humidity, the patient's subjective comfort significantly improved, and the respiratory secretion was more easily discharged; therefore, it could reduce the incidence of lower respiratory tract infection. Moreover, the application of HFNC oxygen therapy could reduce the work of

respiratory muscles, improve patients' oxygenation, reduce energy consumption, and accelerate the recovery of patients' physical condition; therefore, it was beneficial to the recovery of patients. However, due to the small number of cases and poor representativeness in this study, data from a large sample is needed to verify this conclusion.

In this study, all the patients were cured and met the discharge standard of the COVID-19 Diagnosis and Treatment Plan (trial version 7) [1]. Analysis revealed that the length of ICU stay and the total length of hospitalization were shorter in the HFNC oxygen therapy group than in the COT group, and the difference in the length of ICU stay between the two groups was statistically significant. This suggests that the application of HFNC oxygen therapy can reduce the length of ICU stay and the total length of hospitalization. Therefore, as an oxygen therapy strategy widely used in clinics, HFNC oxygen therapy has shown its important role in acute respiratory failure. In this study, we analyzed the recovery of each index after the application of HFNC oxygen therapy and compared it with the COT group. The result suggests that HFNC oxygen therapy has good application value in the treatment of patients with severe COVID-19 and should be promoted in clinical diagnosis and treatment.

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## **Consent for publication**

All participants signed a document of informed consent.

## **Competing interests**

The authors declare that they have no competing interests.

## **Ethics approval and consent to participate**

I confirm that I have read the Editorial Policy pages. This study was conducted with approval from the Ethics Committee of our hospital. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

## **Availability of data and materials**

We declared that materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes, without breaching participant confidentiality.

## **Authors' contributions**

TXB and SY conceived the idea and conceptualised the study. TXB and HMF collected the data. SY and YG analysed the data. TXB and ZL drafted the manuscript, then SY, HMF and SJF reviewed the manuscript. All authors read and approved the

final draft.

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### **Figure Legends:**

Figure 1 RR change trend based on each time point in the two groups

Figure 2 PaO<sub>2</sub>/FiO<sub>2</sub> change trend based on each time point in the two groups