Effect of Pulmonary Rehabilitation on Patients' Outcome After Extubation: A Randomized Controlled Trial

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Research

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Abstract

Background: To evaluate whether pulmonary rehabilitation can improve respiratory function and life quality of the patients who were removed from invasive mechanical ventilation in the ICU and sequentially treated with high-flow humidification therapy instrument.

Methods: This study is a single-center clinical randomized controlled trial. Selected from April 2019 to April 2020, 53 patients who were sequentially treated with High-Flow Humidification Device after extubation in the ICU were randomly divided into two groups. The experimental group received pulmonary rehabilitation treatment, while the control group received only conventional treatment. All patients were then evaluated for rehabilitation and bedside diaphragm ultrasound measurement.

Results: Compared with the control group, experimental group's incidences of non-invasive ventilation use, re-intubation and complication were significantly reduced ($P < 0.05$), yet there was no significant reduction of two groups' mortality rate ($P = 0.3$). The experimental group's MRCsum (Medical Research Council sum) muscle strength score, 30-second sit-up test parameter, and modified Barthel index all presented significant difference ($P < 0.05$). The degree of diaphragm movement, end-inspiratory diaphragm thickness and diaphragm thickness variation rate were significantly increased ($P < 0.05$).

Conclusions: Pulmonary rehabilitation is safe with certain efficacy. It is of great significance to the enhancement of patient's peripheral muscle strength and endurance, respiratory function, and daily life activities. It can reduce the incidences of non-invasive ventilation use and re-intubation and help patients return to their families and society better. Nevertheless, the current development of pulmonary rehabilitation is not perfect. Subsequent research of a multi-center randomized controlled trial should be conducted to further explore the efficacy of pulmonary rehabilitation, promote the spread of pulmonary rehabilitation technics, and provide home-based rehabilitation guidance and long-term follow-up for discharged ICU patients.

Trial registration: Clinical trial registration number: NCT04368286; Ethics number: S2018-212-01.

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Background

With the advancement of medicine in modern society, the survival rate of critically ill patients has gradually increased. The refined respiratory treatment technology and individualized mechanical ventilation strategies have greatly improved the success rate of Intensive Care Unit (ICU) patients' removal from mechanical ventilation. As a routine respiratory supporting method, High-Flow Humidification Device (hereinafter referred to as "High-Flow") is widely used in patients with mild to moderate respiratory failure. Owing to the favorable effect of high-flow humidification and warming, more and more patients choose High-Flow therapy instrument for sequential treatment after withdrawal. However, during hospitalization in the ICU, factors such as braking, mechanical ventilation, use of a large

number of drugs, lack of adequate nutritional support, and lack of family accompany may lead to the occurrence of patients' respiratory and limb dysfunction as well as ICU-acquired weakness [1]. Atrophy of respiratory muscles caused by long-term mechanical ventilation is more likely to expose patients to the risk of endotracheal re-intubation.

Respiratory rehabilitation technic was first used in patients with COPD, aiming to relieve the symptoms of patients in stable phase and improve their exercise ability [2]. In recent years, more and more scholars have noticed that the survival rate of critically ill patients is improved, but it is often accompanied by a sharp decline in quality of life and years of dysfunction left after the ICU [3]. The development of respiratory rehabilitation technic for critically ill patients greatly improved the patient's dysfunction, significantly enhanced quality of life, and promoted patient's prognosis [4]. However, the research of various scholars is highly heterogeneous: some scholars believe that critical-case respiratory rehabilitation technic can ameliorate the anxiety and depression of patients with long-term chronic respiratory diseases, thereby affecting their mortality [5] [6] [7], but some scholars believe that respiratory rehabilitation does not have significant impact on mortality, as mortality should be related to the patient's primary disease and other factors [8] [9].

In order to evaluate the effect of respiratory rehabilitation in critically ill patients, we conducted a randomized controlled trial, focusing on respiratory dysfunction and reduced quality of life that are common in ICU patients, as well as the effect on prognosis.

Methods

Trial Design

This trial is a single-center clinical randomized controlled trial initiated by the investigator, conducted in the Respiratory Intensive Care Unit (RICU) of the Chinese PLA General (301) Hospital in Beijing, and has been approved by the local ethics committee. Each patient participating in the experiment has signed an informed consent.

53 patients who were sequentially treated with High-Flow humidification therapy instrument after extubation in the ICU were selected from April 2019 to April 2020. Inclusion criteria: age 18-95 years; stable hemodynamics, namely, $50 < \text{heart rate} < 120$ beats / min, $90 < \text{systolic pressure} < 200$ mmHg, $55 < \text{average arterial pressure} < 120$ mmHg; at least 2 hours without increasing the dose of vasopressors; intracranial pressure is stable, and there is no seizure within 24 hours; the respiratory state is stable, which means that the patient's finger oxygen saturation is $\geq 88\%$, $10 < \text{respiratory frequency} < 35$ times / min [10]. Exclusion criteria: pregnancy; acute myocardial infarction.

A single-center clinical randomized controlled trial method was used. After the patients who met the criteria were enrolled, the researcher decided patients' grouping according to the random numbers distributed by a random number table. The random number table was only known to the one researcher. The patients assigned to the experimental group were treated with individually formulated pulmonary

rehabilitation program strictly implemented by a professional rehabilitation therapist (Figure 1), while patients in the control group were subjected to conventional medical treatment by physicians. The rehabilitation program was formulated according to the ABCDEF Cluster Management Strategy [11] and the step-by-step Six-Step Exercise and Physical Activity Method [12].

Total Lift Bed training: Using Total Lift Bed (VitalGo®, Fort Lauderdale, USA) and starting pre-tilt training from 30°. If there are no obvious changes in vital signs, increasing the angle by 10° per 10 minutes, with 30 minutes' each training time. It is recommended to start at 40° after one week, and to stop the Total Lift Bed training when the patient can stand or walk independently.

Termination indicators: If the patient's heart rate, systolic blood pressure, and average arterial pressure fluctuate by more than 20%, the rehabilitation treatment shall be stopped and the physician shall proceed with observation. If the indicators can get resumed within 2-3 minutes, then the training shall continue; if they cannot be resumed, the training plan shall be re-evaluated and adjusted.

Measures and Data Collection

Primary endpoint: the evaluation and treatment of pulmonary rehabilitation was initiated after the patients were enrolled in the groups, and the rehabilitation was carried out until the patients were discharged from the hospital. If the patients were exposed to acute cardio-cerebrovascular events or died during the process, the experiment should be terminated.

All patients were monitored for vital signs every day after getting registered in groups, and the data collection was stopped by the 28th day since the patient joined the group. Peripheral muscle strength MRC evaluation, 30-second sit-up test, modified Barthel index, Borg dyspnea score, arterial blood gas analysis and bedside diaphragm ultrasound monitoring were performed at the time of admission and discharge. At last, the patient's following outcomes during these 28 days were counted: whether a non-invasive ventilator was used; whether re-endotracheal re-intubation was performed; whether there were new complications (pressure ulcers, aspiration, thrombosis, etc.). The time when the patient first got out of bed, the patient's length of ICU stay and his/her length of hospital stay were also recorded. In bedside diaphragm ultrasound, 1.4 cm was seen as the normal value for diaphragm movement; 0.15 ~ 0.28cm was regarded as the normal range of diaphragm thickness; 20% was set as the bottom line of the diaphragm thickness variation rate, and thus less than 20% was regarded as diaphragm dysfunction [13] [14].

Statistical Analysis

Statistical processing: using SPSS 21.0 statistical software, the measured data were first tested for normality. Data that met the normal distribution were described by Mean $\pm$ SD, and the difference between groups was described by the independent sample T test; data that did not conform to the normal distribution were described by M (interquartile range), and the difference between groups was analyzed by Mann–Whitney U rank sum test. Counting data was expressed as a percentage, chi-square test was

used for comparison between groups, and the correlation between two indicators was compared using bivariate correlation analysis test. $P < 0.05$ was considered statistically significant.

Results

1. Baseline Data of the Patients

A total of 53 patients were included in this study, including 26 in the experimental group and 27 in the control group. The basic information statistics are shown in Table 1. The two groups of patients were not significantly different in age, gender, APACHE II score and SOFA score (Table 1).

Table 1 Baseline data of patients in the two groups

Information Statistics	Experimental Group (n=26)	Control Group (n=27)	P value: normal (independent sample T test) / non-normal (rank sum test) / count data (chi-square test)
Age (years, Mean±SD)	63.31±23.01	71.22±15.71	0.152
Gender (male:female)	17:9	17:10	0.854
BMI (ratio, Mean±SD)	23.45±5.35	21.81±5.05	0.257
APACHE II (score, Mean±SD)	14.46±7.36	16.89±5.68	0.185
SOFA [score, median (interquartile range)]	7.0(4)	7.0(3)	0.851
Disease Spectrum (cases)			
ARDS	3	0	0.07
COPD	1	3	0.31
High Blood Pressure	0	3	0.08
Diabetes	0	0	-
Cardiovascular Diseases	5	4	0.67
Cerebrovascular Diseases	1	2	0.57

2. Initial evaluation of the enrolled patients before rehabilitation

Statistical test results showed that the experimental group (26 cases) and the control group (27 cases) were not significantly different in MRC, 30-STS, Barthel, Borg, PaO₂, oxygenation index, diaphragm movement, end-inspiratory diaphragm thickness, end-expiratory diaphragm thickness, variability, etc. (Table 2).

Table 2 Initial evaluation of the enrolled patients before rehabilitation

Information Statistics	Experimental Group (n=26)	Control Group (n=27)	P value: normal (independent sample T test) / non-normal (rank sum test)
MRC [score, median (interquartile range)]	39.50±16	38±10	0.305
30-STS [score, median (interquartile range)]	1.50±3	0.00±2	0.118
Barthel (score, Mean±SD)	38.85±18.35	32.96±22.16	0.298
Borg (score, Mean±SD)	4.29±2.29	3.67±2.23	0.321
PaO ₂ (value, Mean±SD)	81.81±18.03	81.93±20.10	0.982
Oxygenation index (ratio, Mean±SD)	277.04±79.93	289.85±106.88	0.624
Diaphragm movement [distance, median (interquartile range)]	1.20±0.66	1.40±0.96	0.262
End-inspiratory diaphragm thickness (thickness, Mean±SD)	0.20±0.07	0.22±0.07	0.325
End-expiratory diaphragm thickness (thickness, Mean±SD)	0.13±0.06	0.06±0.05	0.339
Diaphragm thickness variability (ratio, Mean±SD)	0.52±0.28	0.45±0.23	0.363

3. Primary Outcome

Statistical analysis showed that the experimental group (26 cases) and the control group (27 cases) had significant difference in the incidence of non-invasive ventilator re-use, the existence of new complications, length of hospital stays and the time when patients firstly got out of bed. There was no significant difference in mortality and re-intubation rate, but there were significant differences between the two groups after data correction (Table 3).

Table 3 Primary outcome

Information Statistics	Experimental Group (n=26)	Control Group (n=27)	P value: normal (independent sample T test) / non-normal (rank sum test) / count data (chi-square test)
Length of ICU stay (days, Mean±SD)	16.31±7.18	19.74±10.55	0.171
Length of hospital stay (days, Mean±SD)	18.73±9.76	28.70±20.39	0.028
Time required to get out of bed for the first time [days, median (interquartile range)]	4.00±10	18.00±22	0.000
Non-invasive ventilator use (Used / unused)	2±24	11:16	0.005
Re-intubation (Re-intubated / un-intubated)	3:23	7:20	0.181
Re-intubation (after correction) (Re-intubated / un-intubated)	3±23	11±16	0.000
Mortality (death / survival)	3:23	6:21	0.300
Complications (with / without)	1:25	17:10	0.04

4. Secondary Outcomes

Statistical test results for the post-rehabilitation assessment showed that apart from the parameters of PaO₂ and end-expiratory diaphragm thickness, the experimental group (26 cases) and the control group (27 cases) presented statistically significant difference in Barthel index, Borg dyspnea score, oxygenation

index, diaphragm movement, end-inspiratory diaphragm thickness, and diaphragm thickness variability (Table 4).

Table 4 Secondary outcomes

Information Statistics	Experimental Group (n=26)	Control Group (n=27)	P value: normal (independent sample T test) / non-normal (rank sum test)
MRC (score, Mean±SD)	50.00±9.72	31.37±13.95	0.000
30-STS [score, median (interquartile range)]	5.50[7]	0.00[0]	0.000
Barthel (score, Mean±SD)	69.81±24.56	26.48±24.57	0.000
Borg Dyspnea Score [score, median (interquartile range)]	1.00(2.0)	4.00(5.0)	0.000
PaO ₂ [value, median (interquartile range)]	83.35(15.1)	80.50(24.8)	0.581
Oxygenation Index (ratio, Mean±SD)	348.46±69.84	258.04±111.94	0.001
Diaphragm Movement [distance, median (interquartile range)]	1.46(0.68)	1.06(0.59)	0.016
End-inspiratory Diaphragm thickness (thickness, Mean±SD)	4.29±2.29	4.29±2.29	0.005
End-expiratory Diaphragm thickness (thickness, Mean±SD)	4.29±2.29	4.29±2.29	1.61
Diaphragm Thickness Variability [ratio, median (interquartile range)]	0.53(0.34)	0.33(0.23)	0.001

Discussion

Association with Preamble Studies

When patients were in the state of mechanical ventilation, their diaphragm could shrink and thin in 48 hours, which made the patients dependent on ventilators. ICU-acquired weakness (ICU-AW) occurred in 25%~60% of the cases. However, the incidence of ICU-AW among patients with long-term mechanical ventilation was even as high as 67% [1] [15] [16], which greatly increased the incidence of ventilator-associated pneumonia in patients, and made it difficult to withdraw of ventilation. Pulmonary rehabilitation (or respiratory rehabilitation) is a comprehensive intervention based on comprehensive patient assessment, aiming at treatment for patients, including but not limited to sports training, education and behavior changes, so as to improve the physical and mental health of patients with chronic respiratory diseases, and promote patients' long-term adherence to healthy behaviors [17]. Pulmonary rehabilitation technic is not only effective in COPD patients, but also can be applied to other respiratory diseases, such as lung transplantation [18] [19], lung cancer [20], interstitial lung disease [21], bronchiectasis [22], etc. It can reduce the length of hospitalization, reduce the number of hospitalizations, reduce the symptoms of dyspnea, enhance peripheral muscle strength and endurance, improve the amount of exercise and also patients' quality of life, and can even ameliorate patients' anxiety and depression. Pulmonary rehabilitation conducted at home can further strengthen patients' self-management consciousness [23] [24]. In addition to assessing the improvement of patients' function, this study focused more on the effect of pulmonary rehabilitation on the prognosis of patients in ICU.

Research Findings

The patients included in this study were all patients with invasive positive pressure mechanical ventilation after extubation proved by spontaneous breathing test (SBT) and leak test. There was no significant difference in the assessment of basic vital signs. Diaphragm mobility, diaphragm thickness, and thickness variation rate in all patients were significantly lower than those in normal adults. In addition, 76% of the enrolled patients developed ICU-AW, and 92% could not take care of themselves. It could be due to the massive application of sedation and hormones drugs as well as braking during endotracheal intubation. The patients had a state of exercise intolerance and limited activity level, which is also consistent with previous studies [25]. However, compared with the control group, after the pulmonary rehabilitation treatment was performed, various indicators were significantly improved in the experimental group, and patients' respiratory and limb dysfunction basically got ameliorated. Pulmonary ventilation was closely related to the patient's position. The patients in the experimental group were trained in the sitting position and the standing position at an early stage. The change in position promoted the downward movement of the diaphragm and improved lung ventilation, thereby improving oxygenation and reducing breathing difficulties [26]. Respiratory function and physical activity's mutual promotion ameliorates the patients' dysfunction. In addition, compared with the control group, the experimental group's patients took significantly less time to get out of bed for the first time. On the one hand, the patients in the experimental group received rehabilitation treatment, the concept of which is

early mobility, so these patients had relatively good campaign at the early stage, being able to actively carry out suitable physical activities; on the other hand, early use of electric total lift bed for standing training would not only assist the recovery of patients' cognitive function and improve their level of cooperation, but also promote the recovery of patients' lower limb muscle strength, shortening the time it took to get out of bed by the patients themselves [27] [28].

The main point of this study is to analyze the prognosis of patients. We found that compared with the control group, the incidence of non-invasive ventilator re-use was significantly reduced in the experimental group. At present, High-Flow instrument, as a means of respiratory support, is more and more used in the sequential treatment of patients with extubation. Yet, non-invasive support is stronger than that of High-Flow instrument. If phenomena like respiratory muscle fatigue appeared in the enrolled patients, the doctor would choose whether to perform non-invasive ventilation or tracheal intubation [29], which proved that the patient was in an unstable breathing state at the time, and it might be caused by weakness of the diaphragm. After extubation, the patients in the experimental group received pulmonary rehabilitation treatment, which improved the diaphragm function and reduced the use of non-invasive ventilator. Similarly, there was a significant difference between the two groups in the re-intubation rate after correction. There were 4 patients in the control group who needed emergency intubation, but due to the wishes of their families, invasive ventilation has not been performed, and the actual number of intubation patients in the control group was 11, which made the results statistically different. The diaphragmatic ultrasound and oxygenation index of the experimental group improved significantly, that means, during the pulmonary rehabilitation treatment, the occurrence of respiratory muscle fatigue was avoided, thereby reducing the rate of re-intubation. However, there was no significant difference in the mortality rate between the two groups. The mortality rate was affected by the function of the patient's heart, kidney and other organs as well as the primary disease. Pulmonary rehabilitation could only ameliorate the patient's dysfunction, but could not cure fundamentally, and it had no obvious effect on improving the functions of other organs, so it could not affect the mortality of patients. This is also consistent with previous research results. In addition, the patients in the experimental group enjoyed early mobility, such as sitting training, standing training, etc., which reduced the complications such as pressure sore, aspiration and thrombus caused by braking [30].

Significance of the Findings

The study found that pulmonary rehabilitation can improve the prognosis of patients with extubation. Yet for the elderly patients, pulmonary rehabilitation is a long-lasting process, which takes a long time of treatment to produce significant results, whereas ICU patients are generally subject to a quick referral, so there is no significant impact on their ICU hospital stay, but it can reduce the patient's length of hospital stay and save medical costs. In essence, pulmonary rehabilitation is of great significance to patients.

Strengths and Limitations

Pulmonary rehabilitation can reduce patient's symptoms, improving limb muscle function, exercise ability, quality of life, etc., but its essence is long-term sustained behavior. If the pulmonary rehabilitation

program got stopped immediately after the completion of the initial phase, these aforementioned benefits would then begin to decline in the next 6 to 12 months [31]. Long-term follow-up is needed, but this study did not carry out family follow-up, and thus there is a lack of knowledge and supervision of the patient's rehabilitation at home, and a failure of tracking and analyzing the patient's long-term status. We look forward to adding long-term follow-up mechanism for discharged ICU patients into our next trials.

Conclusions

Pulmonary rehabilitation is safe, and has certain effectivity. It is of great significance to the enhancement of patient's peripheral muscle strength and endurance, respiratory function, and daily life activities. It can reduce the incidences of non-invasive ventilation use and re-intubation, and help patients return to their families and society better. Nevertheless, the current development of pulmonary rehabilitation is not perfect. Subsequent research of a multi-center randomized controlled trial should be conducted to further explore the effectivity of pulmonary rehabilitation, promote the spread of pulmonary rehabilitation technics, and provide home-based rehabilitation guidance and long-term follow-up for discharged ICU patients.

The key message is that we found pulmonary rehabilitation is safe and feasible with no accident events. It can improve patients' prognosis, reduce the rate of re-intubation, shorten the length of hospital stay, and save medical cost for patients. This could change many people's views on the implementation of pulmonary rehabilitation in ICU, raise families' awareness of pulmonary rehabilitation, and promote the development of pulmonary rehabilitation. In addition, it is also safe and effective to carry out early standing training in ICU, in order to reduce complications such as pressure sore and thrombus, and to speed up the improvement of patients' limb and diaphragm function.

Declarations

Ethics approval and consent to participate:

Ethical approval for this study was granted from the Chinese PLA General Hospital. Written informed consent was signed by all study participants. The trial was registered (Clinicaltrials. gov, NCT04368286; ethics number: S2018-212-01), and all procedures were in compliance with ethical standards.

Consent for publication:

Not applicable.

Availability of data and materials:

The dataset supporting the conclusions of this article is included within the article.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

The authors participated in the conception and design of the paper; took the lead in patient recruitment, data collection, data analysis and research interpretation; completed the first draft of the manuscript, and reviewed the important academic content of the manuscript. All authors contributed to the experimental design and data acquisition, contributed to the analysis and interpretation of the data, and read as well as recognized the final manuscript.

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Figures

L0	L1	L2	L3	L4	L5
Hemodynamically stable	Unstable factors i.e. fractures exist	MRCsum score ≤ 36	MRCsum score > 36	MRCsum score ≥ 48	MRCsum score ≥ 48
2hr rollover; Total Lift Bed training	2hr rollover; Total Lift Bed training; Passive joint activity training; Passive power bicycle; NMES	2hr rollover; Total Lift Bed training; Passive bed-chair transfer; Passive joint activity training; Passive power bicycle; NMES	Passive bed-chair transfer; Bedside sitting training; Assisted standing training; Active joint activity training; Upper limb/lower limb resistance training; Active power bicycle (bed); NMES; ADL	Active bed-chair transfer; Bedside sitting training; Assisted standing training; Active joint activity training; Upper limb/lower limb resistance training; Active power bicycle (bed/chair); Walking training; NMES; ADL	Active bed-chair transfer; Bedside sitting training; Standing training; Active joint activity training; Upper limb/lower limb resistance training; Active power bicycle (chair); Walking training; NMES; ADL
Posture drainage; External diaphragm pacemaker	Posture drainage; External diaphragm pacemaker	Traditional physical therapy; Mechanical Insufflation- Exsufflation; expectoration; Breathing out / ACBT; External diaphragm pacemaker; Breathing training	Breathing out / ACBT; Cough; Respiratory muscle retraining	Breathing out / ACBT; Cough; Respiratory muscle retraining	Breathing out / ACBT; Cough; Respiratory muscle retraining

*Note

NMES: Neuromuscular electrical stimulation.

ADL: Activities of Daily Living.

Figure 1

Pulmonary Rehabilitation Program

*Note

HFNC: High-Flow Nasal Cannulas.

Figure 2

Trial process