The Efficacy of High-frequency Chest Wall Oscillation (HFCWO) for the Improvement of Symptoms in Children with Mycoplasma pneumoniae

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August 23, 2020

Abstract

The aim of this study was to evaluate whether high-frequency chest wall oscillation (HFCWO) could improve the symptoms of children with Mycoplasma pneumoniae pneumonia.We recruited 157 children with M. pneumoniae pneumonia between February 2017 and December 2018. We collated clinical data for each subject and then randomly divided the subjects into a control group (n=82) and an HFCWO group (n=75). Subjects in the control group were given azithromycin, budesonide, ipratropium bromide, and salbutamol. The HFCWO group received all of the treatments given to the control group but also received HFCWO. A range of tests were carried out on each group before treatment and 7 days after treatment, including chest X-ray, routine blood tests, C-reactive protein (CRP) levels, and lung function; we also recorded the duration of fever and cough. Treatment efficacy (based on upper respiratory tract symptoms) was better in the HFCWO group than in the control group (P=0.03). Levels of CRP were significantly lower in the HFCWO group. Patients in the HFCWO group also had shorter durations of fever and cough, and shorter stays in hospital (P<0.05). Treatment costs were also significantly lower in the HFCWO group(P<0.05).Relative to predicted values, forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF), were all significantly improved in the HFCWO group(P<0.05). In conclusion, the combination of adjuvant treatment with HFCWO will be of significant benefit to children with M. pneumoniae pneumonia. This treatment combination improves clinical symptoms, reduces the length of hospital stay, and reduces costs.

1. Introduction

Mycoplasma pneumoniae pneumonia is a respiratory disease caused by *M. pneumoniae* infection, and represents a common form of community-acquired pneumonia in children. *M. pneumoniae* is predominantly transmitted via the respiratory tract(1). Severe cases can involve pleural effusion, atelectasis, mediastinal gas, pneumothorax, and necrotizing pneumonia(2). In a small proportion of children, the disease develops rapidly and becomes critical, often accompanied by respiratory distress. These children may require respiratory support,such as oxygen mask inhalation, intubation, ventilator support, or extracorporeal membrane oxygenation for lung support. The disease can sometimes lead to death(3, 4). Many with this form ofpneumonia are affected by the formation of sputum plugs (2).Physical chest therapy, such as manual percussion,is commonly used as an adjuvant therapy to remove sputum (5), although this method is known to be inefficient.High-frequency chest wall oscillation(HFCWO) is a relatively new technique for the clearance of sputum from the chest wall. HFCWO involves an inflatable jacket that is attached to a pulse generator by hoses that enable the equipment to oscillate mechanically at variable frequencies (5–25 Hz).These oscillations are caused by the generator sending air through a hose which causes the vest to inflate and deflate rapidly(6).This technique has been widely used forthe treatment of respiratory diseases, includingpulmonary infection,chronic obstructive pulmonary disease(COPD), and pulmonary fibrosis(6-9).The application of this

technique may improve function and help to reduce a decline in lung function; it may also reduce the need for oral antibiotics, reduce the need for hospitalization, and alleviate hypoxia (10). However, little is known about the efficacy of HFCWO for the treatment of children with *M. pneumoniae*pneumonia. In this study, we analyzed 157 children with *M. pneumoniae*pneumonia in our hospital. Our aim was to provide reference guidelines for clinical treatment.

2. Materials and Methods

2.1 Inclusion and exclusion criteria

We screened a total of 378children (6–12 years-of-age) with *M. pneumoniae* pneumonia who had been hospitalized at Beijing Friendship Hospital affiliated toCapital Medical University between February 2017 and December 2018.Of these, 130 were not eligible, as determined by our inclusion criteria, and 91 declined to take part. Consequently, our final analysis featured 157 children; these children were randomly allocated into a control group (82 patients) and an HFCWO group (75 patients).

The inclusion criteria were as follows:1) clinical manifestations of pneumonia, such as fever and cough;2) radiological changes associated with pneumonia; 3) an antibody titer [?]1:160 in the gelatin particle agglutination assay;4) no treatment prior to admission; and 5) no requirement for immediate oxygen therapy. Patients were excluded if pathogen detection tests suggested that the patient had a combination of infections, if chest radiography showed obvious pulmonary consolidation, if the patient suffered from congenital respiratory problems, or if the patient was unable to complete the lung function test.

The study was approved by the medical ethics committee of Beijing Friendship Hospital affiliated toCapital Medical University (Reference Number: 2017-239) and the parents/guardians of all included subjects provided informed and signed consent.

2.2 Treatment

The control group were administered with azithromycin (Pfizer Ireland Pharmaceuticals, NY, USA) via an intravenous drip (10 mg/kg, once daily),Budesonide Suspension for Inhalation (AstraZeneca Pty Ltd., North Ryde, Australia) by atomization inhalation (2 mg, twice daily), and Compound Ipratropium Bromide Solution for Inhalation (Laboratoire Unither, Espace Industriel Nord, France) by atomization inhalation (1.25–2.5 mL, twice daily). All drugs were administered for 7 days. In addition to the treatment provided for the control group,the HFCWO group also underwent sputum clearance using HFCWO (20 min, twice daily for 7 days, 10 Hz, at a pressure setting of 4) (Talent Medical Electronics Co., Ltd, Zibo, China). In the event of fever, subjects in either group were given ibuprofen (Shanghai Johnson & Johnson Co., Shanghai, China). If children developed expiratory dyspnea and transcutaneous oxygen saturation SO_2¡90%, they were given persistent low flow oxygen therapy (1–3L/min).

2.3 Clinical data collection

Upon recruitment, we acquired a range of clinical information from all patients, including gender, age, clinical data related to illness, time of symptom onset, time of symptom remission,respiratory rate and oxygen supplementation. We then calculated the duration of symptomsas the time from the onset of symptoms to remission. The length of stay(LOS) was determined for all patients, as well as the costs involved.

2.4 Lung function testing

Prior to treatment, and after 7 days of treatment, we tested the pulmonary function of each child using a lung function measurement system (AS-507; MINATO Medical Science Co.,LTD.,Osaka,Japan).We recorded a range of parameters, including theforced expiratory volume in 1 s (FEV1)/predicted value, forced vital capacity (FVC)/predicted value, and peak expiratory flow (PEF)/predicted value. All patients were of Chinese ancestry. The predicted values were calculated by using the published predicted valuesfor children's lung function in Beijing,China(11).

2.5 Imaging and laboratory tests

Chest X-rays,routine blood tests, and C-reactive protein (CRP) tests, were performed immediately on the day of admission and 7 days after treatment. Chest X-rays were compared by a radiologist, who was blinded to the experimental grouping, based on the electronic images of two images taken before and after treatment so as to identify changes in chest abnormalities and create a formal report.

2.6 Therapeutic effects

After 7 days of treatment, we evaluated the efficacy of our treatment plan. The treatment was considered as "effective" if fever, convulsive cough, and other symptoms of the upper respiratory tract,had disappeared. The treatment was considered as "ineffective" if obvious clinical symptoms remained after the treatment had finished, and the chest X-ray suggested no improvement or aggravation (12).

2.7 Data analysis

SPSS 21.0(IBMCorp.,Armonk,NY,USA) was used for all statistical analyses.The Shapiro-Wilk test was used to determine whether data were normally distributed.Normally distributedcontinuous data are expressed as mean ± standard deviation, whilecategorical data are expressed as frequency and percentage. Chi-square tests and independent-sample t-testswere used to compare data between the two groups.

3. Results

3.1 Side effects arising from vibration therapy

Ten children described transient dizziness caused by vibration during HFCWO treatment, although this was well tolerated and disappeared when the treatment had been completed. None of the children experienced side effects, such as an abnormally fast heart rate, shortness of breath, chest distress, or other problems caused by hammer dynamic changes.

3.2 Comparison of baseline data between the HFCWO and control groups

There were 75 patients in the HFCWO group; 53 males (79.7%) males and 22 females (20.3%) with a mean age of 8.01±1.37 years. There were 82 patients in the control group; 62 males (75.6%) and 20 females (24.4%) with a mean age of 7.96±1.37 years. There were no significant differences between the two groups with regards to age, gender, white blood cell count(WBC), respiratory rate or CRP level (P>0.05). Prior to treatment, there were no significant differences between the two groups with respect to FEV1 (79.2±2.51%*vs* 79±2.48%), FVC (83.1±2.74% *vs* 83.4±2.69%), or PEF (82±0.86% *vs* 82±0.85%) (Table 1).

3.3 Comparison of the treatment effects,cost, and length of staybetween the HFCWO and control groups

Following treatment, there were no significant differences in WBC and respiratory ratewhen compared between the two groups. However, the CRP levels of patients in the HFCWO group were significantly lower than those in the control group(7.13+-4.39*vs* 9.53+-1.51 mg/L; P¡0.05).Although there was no difference inrespiratory rate,but high respiration rate matched for age and gender in the HWCO group had significantly less than the contrcol group(10.1%*vs* 23.2%; P¡0.05)Five children required oxygen in theHFCWO group; this was significantly fewer than the 14 patients in the control group that required oxygen (6.67% *vs* 17.07%; P¡0.05). The total effective rate in the HFCWO group (88%) was significantly higher than that in the control group (75.6%; P<0.05). The duration ofcough in the HFCWO group (5.2+-1.2 days) was significantly shorter than that in the control group (5.8+-1.5 days; P<0.001). Furthermore, the duration of fever in the HFCWO group (3.6+-0.93 days) was significantly shorter than that in the control group (5.1+-1.08 days; P<0.001). Following treatment, FEV1 (81.5+-1.67% *vs* 80.3+-2.19%; P<0.001), FVC (85.3+-2.49% *vs* 84.2+-2.67%; P = 0.007), and PEF (85.5+-1.34% *vs* 84.0+-1.05%; P<0.001), were all significantly higher in the HFCWO group than in the control group (Table 2). The proportion of chest X-raysindicating no improvement or aggravation in the HFCWO group(27,36%) was lower than that in the control group(35,42.7%),but the difference showed no statistically significant(P=0.392).The LOS in the HFCWO group was significantly shorter than that in the control group(9.03+-1.81*vs*10.78+-2.49 days; P¡0.001). Finally, the treatment costs in the

HFCWO group were significantly lower than the control group(6263.29+-1727.7*vs*7769.82+-2118.65 yuan; P¡0.001).

4. Discussion

*M. pneumoniae*pneumonia is a pulmonary infection caused by infection with *M. pneumoniae* . The prevalence of*M. pneumoniae* pneumoniais gradually increasing in children. Furthermore, a study involving 27,498 pediatric patients in North China reported that 37.5% of these children had*M. pneumoniae* pneumonia; during the peak of this disease, an epidemic took place every 2–3 years (13). Almost 90% of casesoccur in families that experience multiple cases, and immunity is not long lasting (14). The most common symptoms at onset are fever and cough. These symptoms tend to have a long duration and are prone to re-occur, adversely affecting the respiratory system. Furthermore, *M. pneumoniae* infection can lead to a range of complications, including hemolysis, rash, joint pain, and swelling. In addition, the infection can exert severe effects on the nervous and cardiovascular systems, leading to aseptic meningitis or meningoencephalitis, arrhythmia, heart failure, chest pain, and other severe complications(13, 15-18).

After invading the respiratory tract,*M. pneumoniae* localizes between the cilia and adheres to the surface of epithelial cells via adhesive organelles, thus preventing mucociliary clearance and phagocytosis(19). This effect makes it very difficult for the body to remove sputum containing *M. pneumoniae* and its metabolites.Furthermore,*M. pneumoniae*infection can lead to inflammatory edema in the airways, thus causing the tracheal wall to thicken; this effect is exacerbated by the accumulation of sputum. These factors can have an adverse effect on recovery time (20). Previous research also reported that *M. pneumoniae* adhesion inducesthe synthesis of hydrogen peroxide; this endogenous form of reactive oxygen species (ROS) can cause oxidative stress damage(21). The accumulation of ROS,such as peroxides, in host epithelial cells can lead to damage, including vacuolar degeneration, mitochondrial swelling, cell dissolution, and necrosis(22).

The clearance of sputum is driven by a combination of rhythmic waving of the cilia and coughing; this combination of mechanismsrepresents the body's protective respiratory reflex to remove secretions, or foreign bodies, from the respiratory tract through airflow and vibration(23). In children, *M. pneumoniae* pneumonia weakens ciliary movements and reduces lung function, thus making it very difficult for the body to discharge sputum(23).Therefore, when treating children with *M. pneumoniae* pneumonia, it is very important to provide sputum clearance assistance to promote the effective clearance of sputum containing metabolites of *M. pneumoniae* .This process helps to avoid the development of further complications. A previous study highlighted that the formation of sputum plugs in children with *M. pneumoniae*pneumonia results in significantly poorer chest imaging results and a significant increase in the time required for fever remission (24).

The HFCWO systemcan simulate the physiological process of normal coughing. This system involves anairpulse generatorconnected toan inflatable vest, thus causing the patient's chest wall to vibrate. In a recent review of oscillating devices for airway clearance in patients with cystic fibrosis, the HFCWO system was described as a routine form of treatment (25). In a study of patients with cystic fibrosis combined with exacerbation of chronic pyoobstructive bronchitis, the HFCWO system led to a significant improvement in lung function, as compared with a control group, both in terms of FEV1 (10.0 +- 4.6 *vs* 6.9 +- 3.6% for FEV1; P = 0.04) and FVC (9.5 +- 4.8 *vs* 5.9 +- 3.8%; P = 0.03) (26).The HFCWO system generates directional drainage forces and a vibrating airflow between the lungs and the airway, thus loosening and clearing the sputum by shear force. Furthermore, this system stimulates cilia on the wall of the airways to help move the sputum along the air passage, ultimately helping the patient to discharge the sputum (6). HFCWO is widely used for treating chronic obstructive pulmonary disease and for assisting with postoperative sputum clearance in critically ill patients. Research has shown that HFCWO is effective and helps to recover airway function (25). In a study of patients undergoing single-port video-assisted thoracoscopic surgery lobectomy, Zhu et al. found that FEV, FVC, and PaO_2, were all higher in patients treated with HFCWO than in a control group (27). In a study of bronchiectasis, HFCWO significantly reduced the rate of hospitalization (from 1.3+-1.0 to 0.46+-0.81; P<0.0001), significantly reduced the use of antibiotics (from 2.5+-0.86 to 2.1+-0.92 courses/year; P<0.0001), and reduced the decline in FEV1(from 1.85 +- 0.60 to 1.89 +- 0.60 L) (28), although the latter was not significant. Although HFCWO has been widely used as a clinical treatment,

little is known as to how it might help children with *M. pneumoniae* pneumonia.

The purpose of the present study was to evaluate whether HFCWO could improve the symptoms of children with*M. pneumoniae* pneumonia. HFCWO, which uses high-frequency chest wall vibration to help patients to expectorate sputum, resulted in a total effective rate that was significantly higher than that in the control group.In addition, HFCWO obviously shortened the duration of convulsive cough and fever. Furthermore,compared to the control group, patients receiving HFCWO showed a significant improvement in lung function (FEV1, FVC, and PEF, relative to predicted values). HFCWO also accelerated improvementsin chest X-rays and reduced the length and cost of hospital stays.

There are several limitations to this study that need to be considered. First, because the technology has not yet been popularized, the parents of patients were not very receptive to the technology; this inevitably led to a small sample size. Second, as this form of treatment is still being explored, this research study was only based in a single center. Future research should aim to increase sample size and involve multiple centers.

5. Conclusion

Our findings demonstrate thata combination of adjuvant treatmentwith HFCWO may help children with*M. pneumoniae* pneumonia to achieve clear improvements in clinical symptoms, reduce the length of hospital stays, and reduce costs. Further studies, incorporating multiple centers, are now needed to evaluate clinical efficacy, tolerability, adverse effects, and cost effectiveness.

Acknowledgments

I would like to thank the medical staff at the Beijing Friendship Hospital for their assistance with this research. I would also like to thank Dr.Fu,Dr Shi, and Dr.Wan for assistance with medical records. Finally, I would like to thank the radiologists for assisting with their clinical evaluations.

Author Contributions

WGandPForganized the database, LWperformed the statistical analysis, WGand LWwrote and revised the manuscript, and approved the final version for submission.

Conflict of Interest Statement

WG has no conflicts of interest to disclose.

Funding

This research did not receive any specific form of funding.

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Table 1. Baseline data relating to the HFCWO and control groups	Table 1. Baseline data relating to the HFCWO and co
Variable	HFCWO group (n=75)
Male (n, %)	53,79.7
Female (n, %)	22,20.3
Age (years)	8.01±1.3
FEV1 (%)	79±2.52%
FVC (%)	83.1±2.74%
PEF (%)	82±0.86%
WBC(10^9/L)	6.88±1.78
CRP(mg/L)	15.33±7.63
Respiratory rate(times/min)	21.24±3.37

Key: FEV1 = forced expiratory volume in 1 s/predicted value;FVC = forced vital capacity/predicted value;PEF= peak expiratory flow (PEF)/predicted value;WBC=white blood cell count;CRP=C-reactive protein;Tachypnea=¿25 times/min

Table 2. Comparison of efficacy between the HFCWO and control groups	Table 2. Comparison of efficacy between the HF
Variable	HFCWO group (n=75)
Effective rate(n, %)	66,88
Fever duration (days)	3.6±0.93
Convulsive cough duration (days)	5.2±1.2
FEV1 (%)	81.5±1.67%
FVC (%)	85.3±2.49%
PEF (%)	85.5±1.34%
WBC(10^9/L)	6.30±1.52
CRP(mg/L)	7.13±4.39
Respiratory rate(times/min)	18.95±2.84

Table 2. Comparison of efficacy between the HFCWO and control groups	Table 2. Comparison of efficacy between the HF
High respiration rate(n, %)	8,10.1
Oxygen therapy (n, %)	5,6.67
LOS(days)	9.03±1.81
Treatment cost(Yuan/¥)	6263.29±1727.7

Key: FEV1 = forced expiratory volume in 1 s/predicted value;FVC = forced vital capacity/predicted value;PEF = peak expiratory flow (PEF)/predicted value; LOS=length of stay. High respiration rate in reference to the pediatric respiratory rate and heart rate lower limit, normal range, and upper limit by age.