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Clinical efficacy of non-invasive ventilation combined with Chinese medicine for intestinal regulation in Chinese children with respiratory disorders

Zhi Xiang[1#], Cui Huang[2#], Yanhong Liu[3], Yonggang Zhang[3] and Yi Shen[4]*

[1]Department of Pulmonary and Critical Care Medicine, Huaihua First People's Hospital, Huaihua City, Hunan Province, China
[2]Huangshi Maternity and Children，s Health Hospital, Huangshi, Hubei, China
[3]Department of respiratory and critical care medicine, Fangzi District People's Hospital, Weifang City, Shandong Province
[4]Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China

Abstract: Chinese medicine for intestinal regulation is an emerging method for pediatric respiratory disorders, which has better clinical value when combined with NIV (Non-invasive ventilation). This study aims to observe the clinical efficacy of NIV plus Chinese medicine for intestinal regulation in Chinese children with respiratory disorders. Thirty-nine patients admitted to Huaihua First People's Hospital, between March 2016 and July 2018 were enrolled, including 14 children with chronic hypercapnic respiratory failure, 19 with non-surgical OSAS, 5 with OB and 1 with central hypoventilation syndrome. After NIV, the blood gas carbon dioxide retention and labored breathing were improved, respiratory rate and heart rate were decreased and the feeding condition of some children improved. After NIV treatment, clinical symptoms of children with OSAS were significantly ameliorated. In polysomnography monitoring, the AHI, OAI and SpO_2 were significantly enhanced following NIV. In addition, patients with OB and central hypoventilation had different degrees of improvement of their symptoms. NIV plus Chinese medicine for intestinal regulation alleviate the clinical symptoms and enhances the quality of life of children with chronic hypercapnic respiratory failure. Some children could be transferred out of the intensive care unit and into home mechanical ventilation.

Keywords: Non-invasive ventilation, Chinese medicine for intestinal regulation, home ventilation, chronic respiratory failure, Children.

INTRODUCTION

Over the past three decades, non-invasive ventilation (NIV) has been widely used to treat respiratory failure caused by various conditions (Fedor, 2017). It was originally used to treat adult obstructive sleep apnea syndrome (OSAS); however, it is also currently being used as an effective treatment for many pediatric diseases. Globally, it has been shown that NIV can cure children with severe OSAS, as well as improve acute and chronic respiratory dysfunction caused by various conditions such as neuromuscular diseases (Rose *et al.*, 2015). Mastouri M. *et al.* previously reported the application value of NIV in the Huaihua First People's Hospital in China, suggesting that NIV can effectively improve symptoms related to sleep and respiration disorders in children (Mastouri *et al.*, 2017). According to the theory of "the lung and the large intestine being interior-exteriorly related", the connection between the lung and the large intestine through the meridian forms the collateral relationship between the *yin* and *yang* of the viscera (Lou *et al.*, 2020). The descending of the lung-*qi* is descendent serves to a normal function of the large intestine, and infection in the lungs may result in the occurrence of lung fire and phlegm, giving rise to the dampness in the lungs, the obstruction of *qi* in the lungs, and the large intestine and drug stool, which in turns aggravates the suppression of lung *qi* (Zhao *et al.,* 2014). The *yin*-deficiency, *yang-qi* hyperactivity, or gastrointestinal heat accumulation all can lead to large intestine stagnation, resulting in the disharmony of lung *qi* and then lung failure and depression, accompanied by symptoms such as wheezing, coughing and expectoration (Hu *et al.*, 2019). The function of digestion and absorption promotes the absorption of nutrients, thereby enhancing the body's immunity and promoting recovery (Round and Mazmanian, 2009). Compared with adults, few reports of NIV combined with Chinese medicine for intestinal regulation treating pediatric respiratory disorders, especially domestically, can be found. This study proposes the intestinal regulation method of traditional Chinese medicine enema to treat Chinese children with respiratory disorders (Yi *et al.*, 2020). This method can regulate the gastrointestinal *qi*, eliminate the complications of non-invasive ventilation such as flatulence and heating, expand its application range, and improve gastrointestinal disorders. In this study, NIV combined with Chinese medicine for intestinal regulation was applied in children admitted to the Huaihua First People's Hospital, and its relevant clinical characteristics

**Corresponding author:* e-mail: 6511057@zju.edu.cn #Equal contributions

and efficacy was analyzed, with an aim to provide a basis to better understand NIV and its clinical applications for children in China.

MATERIALS AND METHODS

Materials

We retrospectively reviewed the cases of 39 children admitted to the Huaihua First People's Hospital between March 2016 and July 2018. Of 39 children included, 14 children had chronic hypercapnic respiratory failure, needing long-term respiratory support, 19 had non-surgical OSAS, 5 had OB (all caused by severe pneumonia) and 1 had central hypoventilation syndrome. of the 39 children, 27 were male and 12 were female, with their ages ranging from 1 month to 11 years. The general data of the children are shown in table 1 and the clinical characteristics of children with NIV are shown in table 2. The Ethics Committee of Zhejiang University School of Medicine had approved the protocol of this study (Approved No. of ethic committee: 2016KY-23/139). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration and its later amendments or comparable ethical standards (Shrestha and Dunn, 2020). Of the included children with chronic hypercapnic respiratory failure, six required long-term respiratory support because of congenital laryngeal softening, malnutrition, vocal cord paralysis, growth retardation, Pierre-Robin syndrome, and mucopolysaccharidosis, five of the children with hypercapnic respiratory failure were in the intensive care unit (ICU), four children were in the cardiac ICU (CICU) following surgery for congenital heart disease and one child was in the pediatric ICU (PICU) with severe pneumonia complicated by bilateral vocal cord paralysis, palatal swelling and congenital laryngeal softening. All five children in CICU and PICU had experienced long-term invasive respiratory support. They could be detached from the invasive ventilator for a short time, but long-term NIV therapy was still required in the hospital. The remaining three children with hypercapnic respiratory failure had neuromuscular disease including one case of congenital muscular dystrophy, one case of mitochondrial muscle disease and one case of spinal muscular atrophy.

For the cases of non-surgical OSAS, etiologies included postoperative tonsillar and adenoid hypertrophy, severe tonsillar hypertrophy in the absence of adenoids, side effects of adenoidectomy, simple obesity and comorbid metabolic syndromes such as Prader-Willi syndrome and diabetes mellitus.

Patients with the following conditions were excluded: Weak spontaneous breathing, asystole or apnea, hemodynamic instability, congenital diaphragmatic hernia and inability to adapt to wearing a nasal mask. NIV combined with Chinese medicine for intestinal regulation was provided after the parents' informed consent was obtained.

Data collection

Clinical data of all children were collected, including gender, age, underlying disease, NIV mode and pressure, respiratory rate (RR), heart rate (HR), arterial partial pressure of carbon dioxide before and after the use of NIV in children with severe and underlying disease, changes in sleep monitoring indicators before and after using NIV in children with OSAS, AHI, OAI and SpO_2.

Ventilator type and setup parameters

A BiPAP S/T 30 ventilator (Respironics, N.V.) was used for all NIV cases reported in this study (Salvo *et al.*, 2018). Different ventilation modes were selected according to the tolerance of the children and their underlying diseases. 16 cases received the bi-level positive airway pressure (BiPAP) mode, 19 cases received the continuous positive airway pressure (CPAP) mode, and 4 cases received the S/T mode. S/T mode means that the ventilator automatically senses the signal when the patient stops breathing and then actively aspirates to allow continuous breathing. The pressure was set according to child age, respiratory disease status, airway resistance, breathing frequency, lung compliance and presence or absence of thoracic deformity. In the BiPAP mode, inspiratory positive airway pressure (IPAP) was 8-14 cmH_2O and expiratory positive airway pressure (EPAP) was 4-8cmH_2O. In the CPAP mode, the downward pressure was set to 4-14 cmH_2O. In the S/T mode, breathing frequency was set to 16-22 breaths/minute, depending on the age of the children, IPAP was set to 12-16 cmH_2O and EPAP was set to 4-6 cmH_2O.

Chinese medicine for intestinal regulation

The Chinese medicine "Xuanbai Dachengqi Decoction" enema was given to those with phlegm-heat obstructing lung syndrome (Sun *et al.*, 2020). The prescription includes 30g raw gypsum (decoction first), 10g raw rhubarb, 10g almonds, 15g melon wilt skin, 30g citrus fruit, and 30g magnolia officinalis. The above-mentioned herbs were decocted with 500ml of water until 200ml liquid was remained and cooled to about 37°C for enema. The depth of the anal canal for the enema was about 10cm, once a day. The course of treatment was 3~7 days. The dose and course of treatment were adjusted according to the children's treatment response, to ensure a shaped or slightly loose stool every 2 to 3 days. In the presence of more severe diarrheal symptoms or syndrome changes, obvious spleen and stomach deficiency and disappearance of phlegm, the dose should be adjusted in time or the enema course should be terminated promptly.

Efficacy evaluation

For children with chronic hypercapnic respiratory failure, respiratory rate (RR), heart rate (HR), and level of arterial

Table 1: General information

General information		Number
Gender		Male: Female =27:12
Age		One month-11 years old
Type of disease	Chronic hypercapnic respiratory failure	14
	Non-surgical OSAS	19
	Obliterative bronchiolitis	5
	Central hypoventilation syndrome	1

Table 2: Clinical characteristics of children with NIV

Child characteristics	N	Details	Ventilator mode
≤1 year old with underlying disease	6(male/female: 1:1)	Different degrees of maxillofacial deformities, motor retardation and malnutrition were presented	BiPAP
ICU	5(male/female: 3:2)	Repeatedly failed in disconnection from invasive ventilator support; 4 cases of congenital heart disease, including 3 cases of postoperative diaphragmatic swelling	BiPAP
Neuromuscular disease	3(male/female: 1:2)	Congenital myodystrophy (7 years old), myodystrophy (8 years old), myodystrophy (8 months old)	S/T
Obliterative bronchiolitis	5(male/female: 4:1)	3 cases of adenovirus infection, 2 cases of *Mycoplasma* infection	BiPAP
Tonsil and adenoidal hypertrophy	11 (male/female: 9:2)	7 cases (63%) still had OSAS after surgery; 1 cannot be operated	CPAP
No tonsils and adenoidal hypertrophy	2(male)		CPAP
OSAS Complicated with diabetes mellitus	1(male)		CPAP
OSAS complicated with Prader-Willi syndrome	4(male/female: 1:1)		CPAP
Simple obesity OSAS	1(male)		CPAP
Central hypopnea syndrome	1(male)		S/T

Note: NIV: non-invasive ventilation, ICU: intensive care unit, OSAS: obstructive sleep apnea syndrome, N: amount, BiPAP: bi-level positive airway pressure, CPAP: continuous positive airway pressure, S/T = Automatic spontaneous/timed control mode.

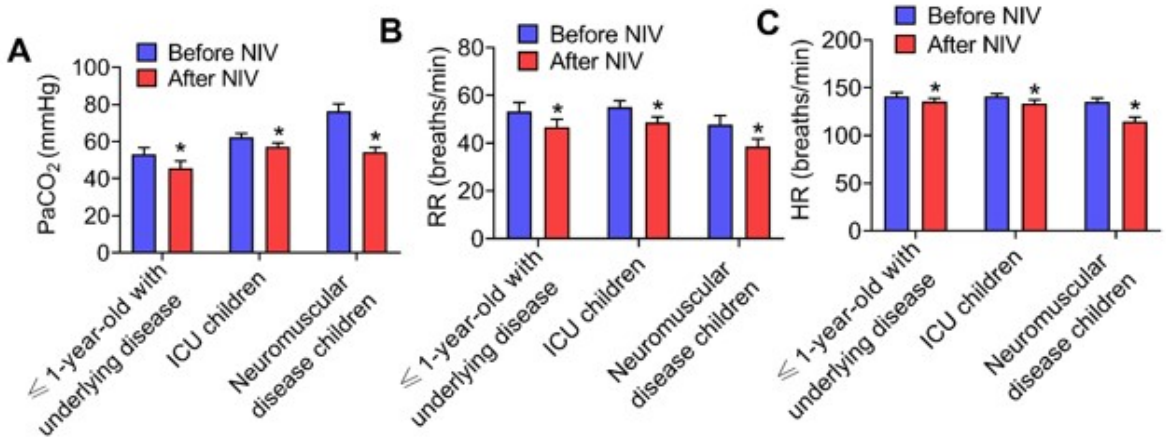

Fig. 1: Comparison of $PaCO_2$, RR, and HR before and after NIV. (A) $PaCO_2$ in different patients before and after NIV. (B) RR in different patients before and after NIV. (C) HR in different patients before and after NIV. NIV: non-invasive ventilation; RR: respiratory rate; HR: heart rate; $PaCO_2$: partial pressure of arterial carbon dioxide.*P<0.05.

Table 3: Efficacy evaluation of OSAS in children

Evaluation of efficacy	AHI(times/h)	OAI(times/h)	Clinical symptoms
Cure	<5	<1	Basic disappearance
Effect	Decrease≥50%	Decrease≥50%	Obvious improvement
Effective	Decrease≥25%	Decrease≥25%	Mitigation
Invalid	Decrease<25%	Decrease<25%	No significant changes

Table 4: Comparison of respiratory related indexes of children NIV treatment

	≤1-year-old with underlying disease			ICU children			Neuromuscular disease children		
	$PaCO_2$	RR	HR	$PaCO_2$	RR	HR	$PaCO_2$	RR	HR
Before NIV	53.17 ±3.72	53.33 ±3.73	141.33 ±3.91	62.26 ±2.11	55.2 ±2.60	140.8 ±3.35	76.33 ±4.15	47.67 ±3.87	135.33 ±4.15
After NIV	45.8 ±3.89	46.67 ±3.36	135.67 ±3.42	57.12 ±2.27	48.8 ±2.22	133.6 ±3.94	54.5 ±2.44	38.67 ±3.08	114.67 ±4.62
t	3.354	3.250	2.669	3.354	3.250	2.669	7.854	3.152	5.762
P	0.007	0.008	0.023	0.006	0.003	0.014	0.001	0.034	0.004

Note: NIV: non-invasive ventilation, ICU: intensive care unit, $PaCO_2$: partial pressure of arterial carbon dioxide (mmHg), RR: respiratory rate (breaths / min), HR: heart rate (breaths/ min)

Table 5: Changes of sleep monitoring parameters before and after NIV treatment in children with OSAS

	AHI	OAI	Minimum oxygen saturation (%)
Before NIV	15-60	10-47	66.28±19.17
After NIV (24 h)	4-10	1.5-3	88.17±3.55
t	3.783	2.559	4.894
P	<0.001	<0.001	<0.001

Note: NIV: non-invasive ventilation, OSAS: obstructive sleep apnea syndrome, AHI: apnea-hypopnea index (times/h), OAI: obstructive apnea index (times/h).

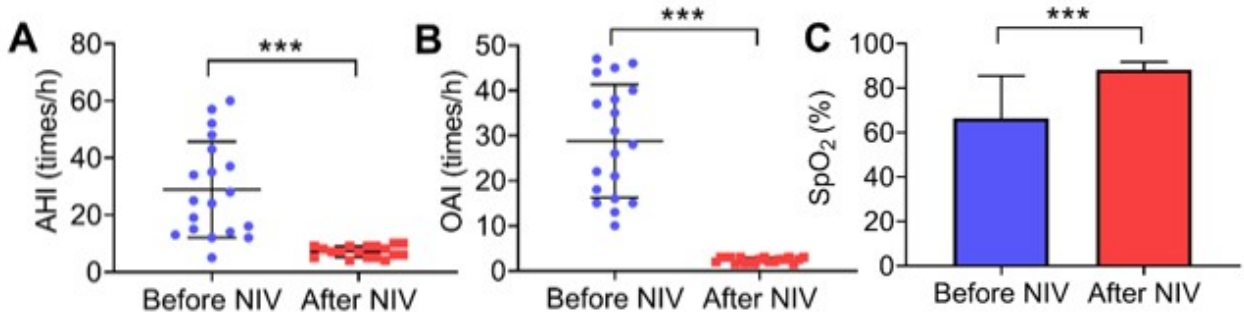

Fig. 2: Comparison of AHI (A), OAI (B) and SpO_2(C) before and after NIV of children with non-surgical OSAS. NIV: non-invasive ventilation, AHI: apnea-hypopnea index, OAI: obstructive apnea index, SpO_2: Minimum oxygen saturation. ****P*<0.001.

blood gas carbon dioxide ($PaCO_2$) were compared before and after NIV treatment and the degree of respiratory failure was closely monitored.

If respiratory failure was exacerbated, timely clearance of airway secretions, tracheal intubation and/or invasive respiratory support were performed.

For children with stable and compatible OSAS, NIV therapy was applied during sleep, and polysomnography was performed before and after NIV. Specifically, AHI, OAI, and minimum SpO_2 were recorded and compared. Ventilator performance was promptly evaluated, especially at first use, including wearing time, minimum SpO_2, the comfort of the children and air leakage after use. Ventilator mode and pressure were adjusted over time to allow for the maintenance or improvement of relevant respiratory function or sleep monitoring indicators.

NIV was compared before and after treatment for various indicators, including the improvement of clinical symptoms, such as snoring, sleep apnea, breathing difficulty and daytime mental status. The laboratory-related indicators for PSG monitoring, including AHI,

OAI, and minimum SpO_2, were compared with those before treatment and the evaluation basis is shown in table 3.

STATISTICAL ANALYSIS

Statistical analysis was performed with SPSS 20.0 for Windows (IBM *Corp.*, Armonk, NY, USA). Measurement data were expressed as the mean ± the standard deviation. The student's t-test was used to compare means. $P<0.05$ was considered statistically significant. As OAI and AHI were not normally distributed, these values were base-10 log-transformed before analysis.

RESULTS

Comparison of indicators before and after NIV application

For children with hypercapnic respiratory failure, RR and HR significantly decreased after NIV use ($P<0.05$, measured after 72h) (See table 4) and their partial pressures of arterial oxygen and carbon dioxide were improved. Specifically, $PaCO_2$ in children with the neuromuscular disease was lower after NIV use (76.33± 3.15 mmHg before NIV vs. 54.5±2.44 mmHg, 72h after NIV) ($P=0.001$), as shown in fig. 1.

For children with non-surgical OSAS, sleep monitoring indicators such as AHI, OAI and minimum SpO_2 were significantly improved after NIV use ($P<0.001$) (as shown in table 5, fig. 2).

Improvement of clinical symptoms

For children with OB, the use of NIV at night stabilized their SpO_2 and improved their breathing frequency, inspiratory depression, energy level and mental state during daytime. Children with central hypoventilation syndrome who had long-term NIV at home had their arterial blood oxygen pressure regularly monitored and were still alive during the 1-year follow-up.

Of the five children in the ICU, invasive ventilators were withdrawn from four children who were then transported to general wards to continue NIV. The remaining child had tracheal intubation due to a lung infection after 72h of use of the ventilator and the child's family member abandoned the treatment because of the aggravated condition. Eventually, NIV was successfully terminated in one patient hospitalization, two patients continued to receive NIV treatment at home and NIV was terminated in all patients by the time of the 3-month follow-up.

DISCUSSION

In recent years, the rapid development of NIV technology has had notable effects on the treatment of respiratory tract obstruction and chronic respiratory failure caused by various pathologies, which has been increasingly applied in adults (Melloni *et al.*, 2018). In pediatrics, NIV has obtained promising efficiency in children with sleep and breathing disorders; however, related research on its application and its efficacy for pediatric patients is little to be found (Behnke *et al.*, 2019). In this study, NIV combined with Chinese medicine for intestinal regulation was used to treat children with different types of chronic respiratory failure, and it was illustrated that NIV combined with Chinese medicine for intestinal regulation improves chronic dyspnea symptoms, shortens the length of hospital stay, and ameliorates patients' quality of life.

Globally, children with neuromuscular diseases are reported as the main recipients of long-term NIV support (Audag *et al.*, 2017). In most cases, these children may have a thoracic deformity or limited mobility which leads to pulmonary ventilation dysfunction. When combined with pulmonary infection, the occurrence of type II respiratory failure can be frequently seen (Panitch, 2017). In the current study, three children with neuromuscular diseases were admitted to the hospital due to pulmonary infection, and the pulmonary infection appeared after treatment, with varying degrees of nocturnal expiratory dyspnea and hypercapnia remained.

According to the application of the theory of "the lung and the large intestine being interior-exteriorly related" in pulmonary diseases (Guo *et al.*, 2014), previous literature pointed out that traditional Chinese medicine decoction or enema is commonly used to relieve the internal organs as pulmonary diseases are considered secondary to disharmony of viscera (Li *et al.*, 2011). Pathological conditions such as stagnant heat accumulation in the large intestine can increase the proliferation of bacteria and toxins in the intestinal cavity and their absorption into the bloodstream, causing damage through intestinal endotoxins (Yao *et al.*, 2017). It has been reported that large-dose intravenous injection of endotoxin in rats can cause acute lung injury (Matute-Bello *et al.*, 2011). Rhubarb can prevent endotoxin from entering the lung tissue, inhibit the accumulation and release of endoneutrophils and alleviate lung damage (Du *et al.*, 2020). The mechanism of the connection between the lungs and the large intestine is essentially an immune regulatory network. The mucosa of the gastrointestinal tract and the respiratory tract are part of the public mucosal immune system and can be transmitted to each other. Mucosal diseases can affect other tissues and organs through mucosal immunity and the secreted IgA (sIgA) is the material basis of this mucosal immunity (Pelaseyed *et al.*, 2014). It is the immunoglobulin most synthesized and secreted by the body, mainly found in exocrine fluids such as colostrum, saliva, gastrointestinal fluid, and bronchial secretions. Moreover, sIgA is also closely related to the occurrence of infectious diseases and immune diseases in the respiratory system and

digestive system, which is of great significance to the diagnosis, treatment and prognosis of related diseases (Li *et al.*, 2020). The study included six children with varying degrees of upper airway obstruction due to congenital laryngeal softening, vocal cord paralysis, growth retardation, and Pierre-Robin syndrome for analysis, with an extremely smaller age (≤1 year old) among the six children than other children and the youngest child was only one month and 24 days old and weighed 3.2kg.

Other conditions in this study included difficulty breathing, feeding disorders, malnutrition, and poor motor development. Five children had OB after severe pneumonia caused by *Mycoplasma pneumoniae* (2 cases) or adenoviruses (3 cases). These children were in the recovery period of severe pneumonia and had symptoms such as persistent wheezing and strenuous breathing after exercise. After they received NIV treatment, their daytime labored breathing was relieved and the exercise ability was enhanced for children of school-going age. In the case of infants, breathing frequency and heart rate decreased after NIV, the duration of pauses during feeding decreased and feeding volume increased. Therefore, NIV combined with Chinese medicine for intestinal regulation alleviates the patients' clinical symptoms and respiratory failure and reinforces their nutritional status, thereby promoting growth and development.

Furthermore, in this study, among five children who were enrolled in ICU, four children with congenital heart diseases were in the CICU after receiving postnatal congenital heart surgery with extracorporeal circulation, as the repeated insertion and removal of the tubes of ventilators and the sole supply of oxygen during the operation result in difficulty in maintaining the infant's respiratory function. There was also a child in the PICU with severe pneumonitis, complicated with bilateral vocal cord paralysis, palatal swelling, and congenital laryngeal softening. NIV (BiPAP mode) was performed for the children in the ICU; four were successfully extubated, but one child in the CICU had to receive tracheal intubation due to pulmonary infection and respiratory failure. After 72h of NIV treatment, $PaCO_2$, RR and HR were improved and SpO_2 returned stable. Thereafter, in-hospital (general ward) NIV treatment was continuously provided. NIV combined with Chinese medicine for intestinal regulation treatment was suspended for two children after the alleviation of the symptoms and two children continued NIV treatment using home mechanical ventilation (HMV). Owing to the mitigation of tachypnea, respiratory failure disappeared by the 1-year follow-up and significant growth and development were observed.

For OSAS without adenoids or tonsillar hypertrophy, or OSAS that remains after adenoidectomy, or OSAS caused by upper airway obstruction, facial dysplasia, obesity, or metabolic syndrome, a radical cure is virtually impossible to obtain by surgery alone, so NIV treatment seems to be more advantageous (Bitners and Arens, 2020). In the current study, the above-mentioned children were polysomnographically monitored before and after NIV treatment and AHI, OAI and minimum SpO2 improved significantly after NIV, suggesting that long-term home application is rewarding. The limitation of this study lies in the small sample size and the combination of cases with differing etiologies. Future studies will expand the size of the case database, optimize multiple follow-up channels, develop long-term follow-up plans, and improve the evaluation system, in order to provide a scientific basis for the use of NIV combined with Chinese medicine for intestinal regulation.

CONCLUSION

In this study, we attempted to provide NIV combined with Chinese medicine for intestinal regulation therapy for children with upper airway obstruction and chronic respiratory failure caused by multiple conditions. We demonstrated that it can significantly improve symptoms, shorten the length of ICU hospitalization, reduce the medical burden on families and make it possible to transfer children to HMV treatment.

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