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Effect of long-term non-invasive ventilation on quality of life and cardiac function of children's neuromuscular disorders with chronic respiratory failure: a clinical trial

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ABSTRACT

Background: Use of long-term non-invasive positive pressure ventilation is increasing greatly worldwide in children with chronic respiratory failure (CRF) of all ages. This treatment requires delivery of ventilation through a non-invasive interface. Cardiac function in majority of these children is impaired. The aim of this study was to assess the effect of institution of non-invasive ventilation (NIV) on quality of life (QOL) and cardiac function in children with CRF related to neuromuscular disorders. Methods: Information obtained from all of the children under 16 years old with CRF due to neuromuscular disorders who were on NIV for at least six months and that were referred to Mofid children's hospital, Tehran, Iran between September 1, 2013, to September 1, 2017.Based on previous studies they were assessed from the year prior to starting NIV and annually thereafter. Data obtained included diagnosis, pulmonary function test, echocardiographic data, length of hospitalizations, and health care costs. Patients and parents completed questionnaires assessing QOL with NIV and recalling QOL one year before commencing NIV. All results were recorded in information forms and data were analyzed with chi square and entered in SPSS 21. Results: Follow-up ranged from 6 to 36 months (median 18). Before and after NIV hospitalization rates (P<0.001), PICU admission (P<0.001) and health care costs decreased respectively. QOL remained stable after NIV despite disease progression (P<0.001). Systolic pulmonary arterial pressure (P=0.009) is diminished. Symptoms of daytime sleepiness (P<0.001) and headache (P<0.001) improved after initiation of NIV. Conclusions: This study revealed that use of NIV results in a reduction in PAH without adverse effects on quality of life and pulmonary function.

Key words: Chronic respiratory failure, Non-invasive ventilation, neuromuscular disorders, pulmonary arterial hypertension, quality of life.

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INTRODUCTION

Non-invasive ventilation (NIV) is the delivery of mechanical ventilation without an endotracheal

tube or tracheostomy [1]. NIV is a well-known treatment in patients with chronic respiratory failure [2]. The earliest forms of non-invasive ventilation put upon negative pressures, such as the "Iron lung" [3]. NIV is used as a first line therapy in wide range of childhood respiratory disorders including upper airway obstruction, musculoskeletal weakness and chest wall restriction, central nervous system disorders and chronic lung diseases [4-6]. The prevalence of children who requiring chronic mechanical ventilation is unknown, but the number has grown over the last two decades [7]. Long term NIV is associated with an increase in survival [8] but its impact on quality of life (QOL) in children is unknown [9]. Home NIV is a practical treatment modality that offers, as compared to prolonged hospitalizations, better QOL and lower costs for children dependent on ventilation technology [10].

The increasing number of patients with pulmonary hypertension (PH) due to alveolar hypoventilation is of particular concern. The pathogenesis of PH in these patients is unknown [11]. It is hypothesized the use of NIV is associated with improved haemodynamics and PH in chronic respiratory failure.

In Iran the use of NIV in children with CRF is very limited and also in our knowledge there isn't any study on these patients in Iran. The aim of this research is to study the impact of NIV on quality of life and pulmonary hypertension in children's neuromuscular disorders with CRF.

MATERIALS AND METHODS

Research design and setting

This study is a before after clinical trial which is conducted in Shahid Beheshti University of Medical Sciences in Mofid children's hospital, Tehran over a four years' period; starting from September 2013 until September 2017.Inclusion criteria included all patients commencing NIV for chronic respiratory insufficiency associated with neuromuscular disorders who was referred to pulmonology clinic of Mofid Children's Hospital during the period September 1, 2013, to September 1, 2017.These children had NIV at least for six months. The criteria for starting of NIV was nocturnal hypercapnia (PCO2>55), and stability of general conditions. Exclusion criteria were patients with chronic respiratory insufficiency and neuromuscular disorder who need intra-tracheal intubation or tracheostomy.

Intervention

Records were reviewed and data obtained from the year prior to usage of NIV and annually thereafter. Data obtained included diagnosis, age of starting NIV, mortality, patient symptoms, growth percentiles, presence of scoliosis, results of pulmonary function testing, overnight oximetry, number of hospitalizations, number of days in hospital and intensive care, and costs to the health service. Pulmonary function testing was performed annually in all children able to cooperate, in a seated or erect position and supine position using a Ganshorn 2011 Spirometer. Echocardiography performed for all of the patient before and immediately after commencing of NIV and three monthly thereafter using Maestro my lab echocardiograph.

Total costs associated with outpatient visits and hospital admissions before starting of NIV were calculated. These were got from the finance departments of the tertiary hospital and local hospitals. Costs after NIV included instruments and specialized nursing fees.

The QOL obtained using the Pediatric Quality of Life Inventory (PedsQL), developed by Dr. James W. Varni (12). Children and parents evaluated separately with the PedsQL version 3.0 (PedsQL 3.0) which was specialized for children's neuromuscular disorders. Different versions of the PedsQL were used in the following age groups; toddler, 0 to 2years; young child, 3 to 7 years; child, 8 to 11 years; and teenager,12 to 18 years. Scores were converted to a 0 to 100 scale, with higher scores indicating lower QOL. In this setting parents completed three sets of questionnaires: one recalling what life had been like for their child one year preceding to start of NIV and one at the month that NIV had started and one after commencing NIV.

Outcome

The commencement of NIV for all patients was in Mofid tertiary hospital. Discharge of patients from hospital had performed step by step and after assurance of appropriate after-care. All the subjects were followed monthly thereafter. In each follow up session subjects underwent ABG check and pulse-oximetry. Then NIV equipment was titrated. They underwent echocardiography each three months. Skills of parents or caregivers

in each visit were evaluated and basic life support was instructed to them. At the end of study data of echocardiography, QOL, symptoms of respiratory failure, ABG and costs of hospitalization and treatment were obtained and compared with the data that had been obtained before NIV.

Statistical methods

Statistical analysis was conducted using SPSS21 software (SPSS, Inc., Chicago, IL, USA). all data of patient was entered to this software and evaluated. Also we used T-test,x^2and fisher test for analyzing data.

Research ethics

The Ethic Committee of Shahid Beheshti University of Medical Sciences confirmed this study (ethic code: IR.SBMU.MSP.REC.1395.539). All patients were informed about this study and its complications, and each patient parent or caregiver provided written informed consent before enrolment.

RESULTS

From sixteen patients, fifteen were enrolled in study and one was excluded because that patient did not come back again. In this study 7 patient were female (47%) and 8 were male (53%). The mean of patient's age was 10.1±4.9 years old. The cause of chronic dependency on mechanical ventilation was respiratory pump disorder. Diagnosis included multiminicore disease (three children), congenital myopathy (two children), Nemalin myopathy (one child) which were confirmed by muscle biopsy. Congenital scoliosis (two children), myopathy with unknown etiology (two children), MERRF syndrome (one child), Myasthenia gravis (one child), progeria (one child), diaphragmatic paralysis (one child) and mucopolysaccharidosis (one child) were other diagnosis in this study (Figure 1). In 73.4% of children parents were close relatives by blood.

Initial assessment

The mean arterial oxygen pressure before commencing NIV was 46.3±13.3 mmHg and peripheral blood saturation was below 90%. After commencing of NIV none of the patients required oxygen supplementation (SPO2>94%) (Table 1).The mean arterial carbon dioxide pressure preceding use of NIV was 81.9±16.6 and this value after starting NIV was decreased to 55.1±7.4 (P<0.001) (Table 1). The mean diurnal time of NIV use was 9.5±9 hours and mean overall length of follow up was 17.7±8.5 months (table 1).All the patients had used Bi-PAP. The interface of NIV for 13 patients was oropharyngeal mask and 2 remaining used nasal mask.

Hospitalization, ICU admittance and healthcare costs

The mean episodes of hospitalization in 2 years' period before starting NIV was 4.2±3.8 which was decreased to 0.4±0.9 (P<0.001) (table 1).ICU admit in 2 years' period before commencing NIV was 13.6±12 days which was decreased to 0.0±0.0 (P<0.001). The mean hospitalization time for respiratory illnesses in 2 years' period before NIV was 28.2±19.7 which was decreased to 0.6±0.8 (P<0.001) (table 1).The mean daily direct cost of health care per patient decreased from 3980 US Dollars in the year prior to institution of ventilation to 0.2 US Dollars in the year following NIV (P= 0.002) (table 1).

QOL score

The mean total QOL score of patients one year before NIV was 33.7±13.1, this score at the time of starting NIV was 51.2±18.3 and one year after commencing NIV the mean total QOL score was 40.5±12.4 (Table 1). Findings showed a significant increase of total QOL score one year before starting NIV compared to the time of commencing NIV (P<0.001) and significant decrease of total QOL score at the time of commencing NIV compared to one-year after starting NIV (P<0.001) but there was no significant statistical difference between the mean QOL score one year before and one-year after NIV (P=0.462).

The mean total QOL score as reported by parents was 35.3±16.3 one year before starting NIV, this score at the time of starting NIV was 58.3±13.0 and the mean QOL score as reported by parents one year after commencing NIV was 42.4±14.1 (Table 1). Findings showed a significant increase of total QOL score reported by parents one year before starting NIV compared to the time of commencing NIV (P<0.001), significant decrease of total QOL score reported by parents at the time of commencing NIV compared to one year after starting NIV(P<0.001) and an increase of the mean total QOL score reported by parents one year before compared to one year after commencing NIV (P=0.040).

Table1. Comparison between results of study before and after NIV

Variable	Before NIV*	Time of starting NIV	After NIV	P value
PO2	--	46.3 ± 16.3 mmHg	> 80mmHg	--
SPO2	--	< 90%	>94%	--
PCO2	--	81.9 ± 16.6 mmHg	55.1±7.4mmHg	P< 0.001
Mean episodes of hospitalization	4.2±3.8	--	0.4±0.9	P<0.001
PICU admission	13.6±12	--	0.0±0.0	P<0.001
Mean daily direct cost	3980 US Dollars	--	0.2 US Dollars	P=0.002
QOL score child report	33.7±13.1	51.2±18.3	--	P<0.001
QOL score child reports	--	51.2±18.3	40.5±12.4	P<0.001
QOL score child reports	33.7±13.1	--	40.5±12.4	P=0.462
QOL score parent reports	35.3±16.3	58.3±13.0	--	P<0.001
QOL score parent reports	--	58.3±13.0	42.4±14.1	P<0.001
QOL score parent reports	35.3±16.3	--	42.4±14.1	P=0.040
Daytime headache	73%	--	0%	--
Daytime drowsiness	66%	--	0%	--
Ability to perform PFT in older than 6 years	0%		90%	

*Before NIV for QOL was one year before starting NIV and for hospital and PICU admission was two years' period before starting NIV

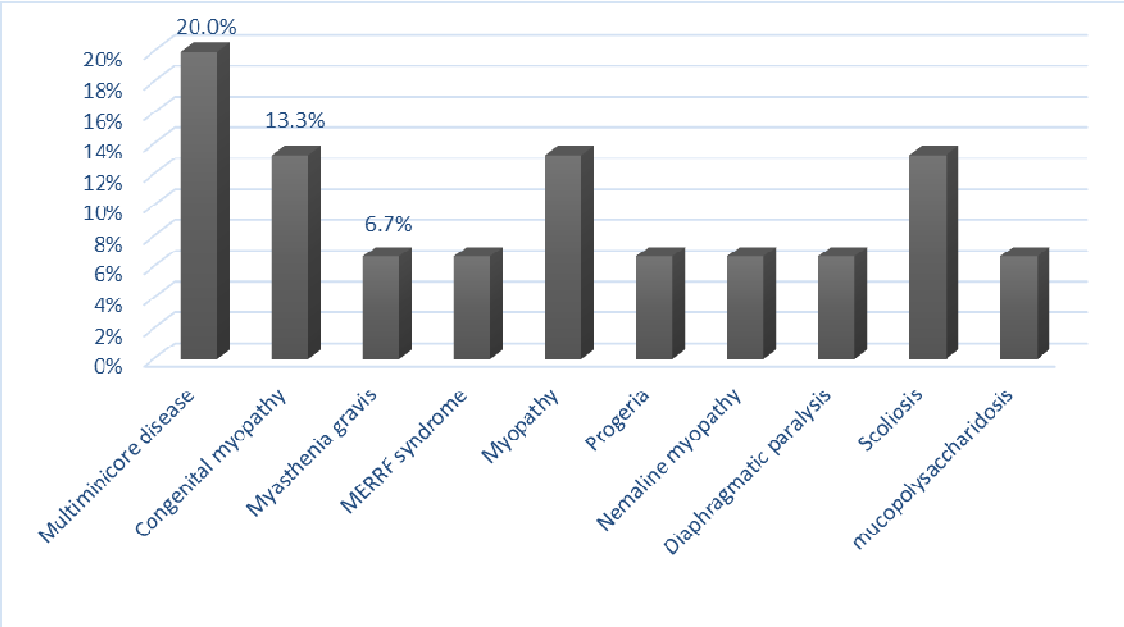

Figure 1. Distribution percentage of Diagnosis in children with neuromuscular disease who need NIV

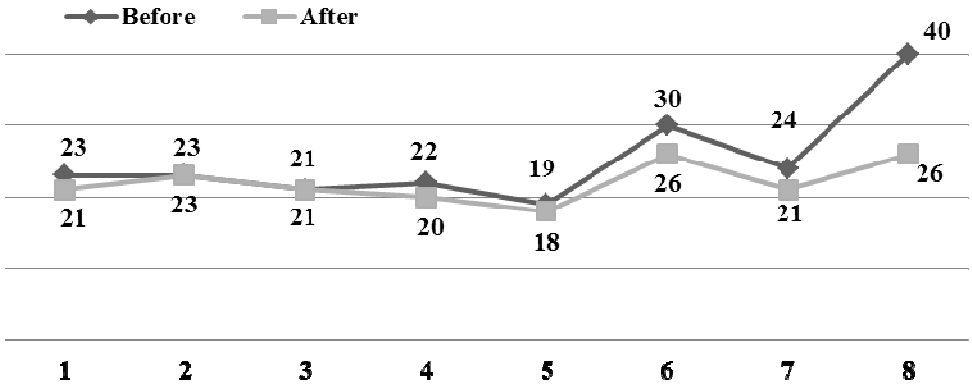

Figure 2. Effect of NIV on mean pulmonary artery pressure

Symptoms and pulmonary function

Eleven patients before starting NIV was suffered from headache but after commencing NIV there were no patients with headache (Table 1). Fourteen patients had drowsiness before NIV but this symptom had relieved totally after starting NIV (Table 1). Ten patients were over six years of age. None of them had the ability to perform pulmonary function testing (PFT) before starting NIV but after commencing NIV nine patients had the ability of performing PFT and only one patient could not perform PFT. In those patients who performed PFT, repeat PFT showed no change in pulmonary function after NIV (Table 1).

Echocardiographic findings and cardiac drug doses

All patients underwent echocardiography before and after commencing NIV. Abnormal findings in left heart were intraventricular septal in diastole in 2 patients, posterior wall in diastole in 2 patients, mitral regurgitation in 4 patients. These data were not changed before and after NIV. The most significant finding in right heart was systolic pulmonary hypertension in eight patients (53.3%). The systolic pulmonary artery pressure in them before starting NIV was 47.9±12.6 mmHg which was decreased after commencing NIV to 40.0±7.0 mmHg (P=0.009) (Figure 2). Also eight patients had increased mean pulmonary artery pressure. The mean pulmonary artery pressure in them before starting NIV was 25.3±6.8 which was decreased to 22.0±2.8 (P=0.084) (Figure 3). All patients with pulmonary hypertension (8 patients) were prescribed drugs (sildenafil and furosemide) which in 4 patients doses of these drugs were decreased to half and in 4 other patients' prescription were discontinued.

Complications of NIV

Overall 8 patients (53%) had no complications. Seven had erythema of nasal bridge one had mask intolerance and one inappropriate fixation.

DISCUSSION

This study was done in Mofid children's hospital which was a major referral hospital in Iran and by far there was no similar study in this age group of Iranian children in our knowledge. The evaluation of cardiac outcome in this study was the new and important concept. Initiation of NIV in children's neuromuscular disorders resulted to decreased healthcare cost, hospital and ICU admissions without adversely affecting pulmonary function and QOL. Also mean and systolic pulmonary pressure was decreased and drug doses that prescribed for PH were decreased significantly.

The majority of studies in the world had done on similar number of patients, age ranges and periods. Castro-codesal et al in a scoping review in 2017 in Canada showed from 289 studies 10% were subject interventional before-after studies with mean period of 25 months. The overall median sample size included studies was 14 (range 3-658) [4]. Patient symptoms including headache and daytime somnolence improved. This has also been shown in another before-after study which H.K. Young et al. in 2007 in Australia were demonstrated that from 14 patients 9 had daytime somnolence prior to NIV. Four also had morning headache. After NIV nobody had daytime somnolence and only one had headache [9]. All patients had hypoxemia before NIV (PO2 < 64 mmHg) however none of the patients required oxygen supplementation after the start of NIV (SPO2>94%). In a respiratory review Sarah L

Morley et al in 2016 in England showed that NIV with lowering work of breathing and oxygen consumption has been reduced the fatigability of respiratory muscles [3].

This study showed use of NIV in children's neuromuscular disorders reduces the frequency and days of hospitalization which in addition to lowering the healthcare costs and support of family resources, it releases pediatric intensive care unit beds that for needy patients is worthwhile. This was confirmed with other studies [7,13]. Cancelinha et al in a retrospective analysis in 2015 in Portugal showed that small number of hospitalization was seen in majority of patients after NIV treatment also high possibility of attending school are good indicator of improvement in quality of life [7]. Katz et al in a retrospective review in 2004 in Canada showed a significant decrease in PICU admission and hospitalization after NIV in children with neuromuscular disease [13].

Patients in this study had progressive neuromuscular impairment it could be expected that their QOL would get worse with increasing age but that did not happen. Our study showed that QOL worsened at the time of starting NIV compared to one year before but QOL improved after NIV compared to the time of starting NIV. So it is hypothesized that NIV may prevent QOL from worsening.one study showed that QOL remained stable after NIV despite disease progression. Young et all in a before after clinical trial in 2007 in Australia showed that QOL remained stable after NIV despite disease progression [9]. In that study 79% of parents completed parent report forms from both QOL questionnaires before and after NIV and only 50% of children completed child report however.in our study all the parents and children participate in completing before, at start and after NIV report forms. In another study Noyes et al in retrospective qualitative study in 2006 in England evaluated QOL after Institution of NIV in children with neuromuscular disease and showed better feeling of these children [14]. In another study Piepers et al in a review of literature in 2006 in the Netherland found that NIV is useful in the longevity and quality of life [15].

Pulmonary hypertension is a consequence of hypoventilation. Current guidelines recommend treatment of the underlying disorder for PH occurring due to lung diseases orventilatory disorders [11]. This study reveals that 53% of patients had pulmonary hypertension before starting NIV and despite lack of complete improvement after NIV the intensity of PH was decreased significantly. In one non clinical study Shekerdemian et al in 1999 in Canada showed that NIV by preventing of exacerbating factors of PH such as hypoxia, hypercapnia, acidosis and atelectasis can be effective in treatment of PH [16]. In our study hypoxia, hypercapnia and work of breathing were relatively corrected and can help in management of pulmonary hypertension. In another retrospective study on 18 subjects in adult population with PH and hypoventilation by Held et al in 2014 in Germany they showed that after 3 months NIV therapy, PAP and PVR decreased significantly. To our knowledge, this is the first study to demonstrate relation between PH, hypoventilation and NIV in children.

In our study nobody had the ability to perform pulmonary function test before starting NIV. However, after commencing NIV spirometry showed severe restrictive pattern which regarding to causes of hypoventilation it seems logical. This issue supposed that NIV with decreasing work of breathing and muscular fatigue can improved pulmonary function. Kallet et al in a literature review in 2009 in US showed that NIV has significant effect on reducing WOB but not found that NIV improved muscle strength or spirometry [17].

This study showed that complications of NIV were mild and the most prevalent of these were erythema of local skin. In another study Ramirez et al in a descriptive study in 2012 in France found erythema of nasal skin with air leak was the major side effect of NIV interface [18].

This study also showed the health care costs after NIV in comparison with PICU hospitalization were decreased significantly. This reduction even with those who had insurance was significant (64%). In another study Young et all in a before after clinical trial in 2007 in Australia also confirmed reduction of health care costs [9].

CONCLUSION

Use of home NIV in children with neuromuscular disorders results in reduction in hospitalization, healthcare costs and PICU admission. This will increase participation of child and family in social interactions such as school, sport, etc. Also NIV

causes longevity and stability of quality of life in these children despite the progressive disease. Also administration of NIV can stabilized pulmonary function test. NIV decreases work of breathing and that can improve growth and nutrition of patients. The side effects of NIV are mild and the majority of these children can tolerate it. NIV can be reduced pulmonary hypertension in children with neuromuscular disease with hypoventilation.

Limitation

Since it was not possible in our centre to carry out polysomnography for children, so only two patients had polysomnography from other centers before commencing NIV. Indication of electively starting NIV was determined better if we could perform polysomnography before NIV. We knew that the best diagnostic tool for evaluation of severity of PH is right cardiac catheterization but we didn't perform that because the procedure is invasive.

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Conflict of Interest

The authors have no conflict of interest to disclose.

Authors' Contribution

Saeed Sadr developed the study concept and design and the acquisition of data, interpretations of data, and drafting of the manuscript. Seyed Ahmad Tabatabaii, Ghamartaj Khanbabaee, Ali Azimi, Mohammad Reza Khalilian, Elham Zarghami, Yalda Nilipour and Mohammad Reza Sharif developed the protocol, analysis of data and drafting of the manuscript.

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