Changing Patterns For The Introduction Of Non-Invasive Ventilation In Children With Neuromuscular Disease

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Abstract

AIM: To review clinical practice for the initiation of home non-invasive ventilation (NIV) in children with neuromuscular disease (NMD)

METHODS: Chart review of all children with NMD initiated on home NIV over a 16-year period (27 May 1995 - July 1 2011). Patients were divided into ‘baseline’ and ‘recent’ groups to assess for changes in clinical practice.

RESULTS: Forty-four patients were studied (mean age 12.7yrs, SD 4.8). NIV use increased over the study period (1.4 NIV initiations/yr in ‘baseline’ group vs. 4.9/yr in ‘recent’ group, $p < 0.0001$). Patients in the ‘baseline’ group had more advanced respiratory insufficiency (awake pCO_2 58.3 vs. 46.3mmHg, ($p= 0.016$)). More patients in the ‘baseline’ group started NIV at the stage of diurnal hypercapnic respiratory failure (10 of 14 (71%) vs. 8 of 30 (27%), $p = 0.008$), while nocturnal hypoventilation with daytime normocapnia was the most common indication in the ‘recent’ group (14 of 30 (47%) vs. 2 of 14 (14%), $p= 0.049$). Severe respiratory tract infections or atelectasis was the primary indication for NIV initiation for 6 of 30 (20%) in the ‘recent’ group compared with 0 of 14 (0%) in ‘baseline’ group. All children in the ‘baseline’ group had NIV initiated in the intensive care unit. In the ‘recent’ group, 24 of 30 children (80%) were assessed as clinically stable and had NIV initiated on the respiratory ward without any major adverse events. The average length of hospital admission for NIV establishment was 6.9 days in the ‘baseline’ group and 3.5 days in the ‘recent’ group ($p = 0.004$).

CONCLUSIONS: NIV is increasingly being used to treat children with NMD, and it is being initiated at an earlier stage in the progression of respiratory insufficiency. For clinically stable children, NIV can be safely initiated on the ward avoiding intensive care admission.

INTRODUCTION

Progressive respiratory failure is the inevitable consequence of many childhood neuromuscular diseases (NMD). In children with NMD, respiratory failure results in significant morbidity and is the major cause of hospital admissions and early death.1, 2 While respiratory failure most commonly develops slowly over the course of several years, it can also present acutely, often in the setting of a respiratory tract infection (RTI).3

In children with NMD, respiratory dysfunction is aggravated by sleep-related reductions in respiratory muscle tone, central drive and arousal thresholds. As a result, diurnal respiratory failure is usually preceded by nocturnal hypoventilation, which develops initially in REM sleep and then in non-REM sleep as the underlying disease progresses. 3-9 Nocturnal hypoventilation leads to hypoxemia and hypercapnia, which stimulate arousals and interfere with sleep quality. Untreated, nocturnal hypoventilation may also contribute to development of daytime respiratory failure through the downregulation of ventilatory responses to hypercapnia.4, 10

Daytime symptoms of nocturnal hypoventilation in children are often non-specific and may be attributable to other aspects of NMD.11-14 As a result, these symptoms may be appreciated only once corrected by treatment.11, 12 There is a poor correlation between diagnosis of nocturnal hypoventilation on polysomnography (PSG) and symptoms.13, 15 Pulmonary function tests and arterial blood gas values fail to predict nocturnal hypoventilation with clinically useful degrees of accuracy.4, 14, 16, 17 PSG remains the gold standard for diagnosing nocturnal hypoventilation, but it is time-consuming, expensive, and its

availability is limited in many settings.

Nocturnal non-invasive ventilation (NIV) has been established as an effective therapy for respiratory insufficiency in children with NMD. NIV normalizes gas exchange,18-22 reverses sleep-disordered breathing and nocturnal hypoventilation,2, 18, 23 reduces the frequency of RTIs/hospital admission,22, 24-28 improves quality of life,2, 22, 25 and prolongs survival.21, 29-31

Two randomized controlled trials (RCT) have examined the timing of NIV initiation in NMD. The first of these found that 'preventative' NIV seemed to lower survival rates in a population of patients with Duchenne muscular dystrophy.32 While this study is much-quoted, it has been criticized because of important methodological flaws.33 The other RCT, of a small heterogeneous population of adults and children, supported nocturnal hypoventilation as an indication for NIV initiation. 2 Nonetheless, despite extensive international experience, there remains a paucity of high-level evidence to inform criteria for NIV initiation.11, 34

The aim of this study was to describe the clinical characteristics of NMD patients started on bi-level NIV since the establishment of a home NIV program at our institution, and to document the practice of NIV initiation.

METHODS

Subjects

The home NIV program for children with NMD was established at the Royal Children's Hospital (RCH) in May 1995. We conducted a single-centre chart review of all children with NMD commenced on nocturnal bi-level NIV, with the intention to continue this therapy at home, between 27 May 1995 and 1 July 2011. RCH is a pediatric tertiary referral centre that services the majority of children with neuromuscular disease from the Australian states of Victoria, Tasmania and southern New South Wales, a combined population of over six million. Patients were identified from the Health Information Services database using International Classification of Diseases (ICD-9 and ICD-10) diagnostic codes corresponding to NMDs and NIV. All patients included in this review had been formally assessed by a pediatric neurologist, and their neuromuscular diagnosis confirmed at the histopathological and molecular level where applicable.

Data collection

For each patient, data collected included demographic information, (age, gender, neuromuscular diagnosis), clinical information at the time of NIV initiation (forced vital capacity (FVC), wake pCO2, PSG result, clinical indication for NIV initiation, presence or absence of daytime symptoms), and information about the NIV initiation process (date of admission and discharge, setting, adverse events).

In cases where NIV was initiated during an acute respiratory decompensation, the most recent well FVC and pCO2 measurements from the previous 12 months were used.

Data analysis

For the purpose of data analysis, subjects were divided into three groups based on neuromuscular diagnosis (Duchenne muscular dystrophy (DMD), spinal muscular atrophy type 2 (SMA 2), and other), and also into 'baseline' and 'recent' groups according to date of NIV initiation. The 'baseline' group comprised those patients initiated on NIV during the first 10 years of the program at RCH (27 May 1995 to 27 April 2005), and the 'recent' group those patients initiated on NIV from 28 April 2005 to 1 July 2011. This time period division was chosen because 28 April 2005 corresponded with a change in local practice, whereby stable children were started on NIV on the respiratory ward, rather than the pediatric intensive care unit (PICU).

Data were analysed to assess differences between the diagnostic groups and for changes in the practice of PSG referral and NIV initiation. Statistical significance was tested using Fisher's exact test for proportions and Student's t-test for means.

Pulmonary function and blood gas testing

Pulmonary function was measured in children over 5 years of age according to ATS/ERS standards using a Jaeger MasterScreen body plethysmograph (Jaeger v4.67, Würzburg, Germany).35 Predicted values were derived from published data.36 In cases with significant scoliosis or where height could not be directly measured, height was derived from ulna length or arm span.37-40

With the exception of one case for which an arterial specimen was used, pCO2 was measured on venous or capillary blood specimens, reflecting hospital policy to minimize arterial punctures in children. Testing was conducted on awake patients during daylight hours, and in room air in all except one case where the patient had been

receiving long-term supplemental oxygen at the time of blood sampling. Blood pCO2 was measured using the automated Bayer RapidLab 1200 blood gas analyser (Bayer, Leverkusen, Germany). Hypercapnia was defined as pCO2 > 45mmHg for arterial or capillary blood gas specimens, and pCO2 > 50mmHg for venous blood gas specimens.41, 42

Polysomnography

PSGs were performed using Compumedics S-series and later Compumedics E-series. Data collected included frequency and duration of apneas and hypopneas, continuous transcutaneous CO2 (TcCO2 mean and peak), continuous pulse oximetry (mean and minimum SpO2), respiratory disturbance index (RDI), rapid eye movement sleep (REM) RDI, obstructive and central apnea/hypopnea indices (OAHI and CAHI). The RDI defined the number of abnormal respiratory events (obstructive or central) per hour of sleep. Prior to 2007, nocturnal hypoventilation was defined as either peak TcCO2 > 53mmHg or TcCO2 > 45mmHg for > 60% of total sleep time (TST).43 Following the publication of the American Academy of Sleep Medicine manual in 2007, the definition was revised to TcCO2 > 50mmHg for > 25% of TST or ≥ 10mmHg increase in TcCO2 during sleep in comparison to an awake supine value. 44 The reporting clinicians had some scope for clinical judgement in cases of suboptimal signal quality.

Ethics approval

Ethics approval for this study was obtained from the RCH Human Research Ethics Committee (HREC 31237 A)

RESULTS

Forty-four patients (32 male) were studied, with a mean age at NIV initiation of 12.7 yrs (SD 4.8 yrs; range 0.8 - 18.8 yrs). Sixteen patients had DMD, seven had SMA 2, and the remainder had other neuromuscular diagnoses (see table 1).

FVC and pCO2 results were available for 36 (82%) and 30 (68%) patients respectively. Six of the eight patients who did not have a FVC result recorded were too young to complete pulmonary function testing. Sixty of 66 FVC and pCO2 results were from within 6 months of NIV initiation (and all were from within 12 months). With reference to all patients, the mean FVC was 30.6% predicted and the mean pCO2 was 51.1mmHg.

Fourteen children were started on NIV during the first 10 years of the program (1995 - 2005), and 30 children commenced during the more recent period (2005 - 2011). This equated to 1.4 NIV initiations per year in the 'baseline' group compared with 4.9 per year in the 'recent' group ($p < 0.0001$). When compared with the 'recent' group, the 'baseline' group had more advanced restrictive lung disease as evidenced by higher awake pCO2 levels (58.3 vs. 46.3mmHg, $p = 0.016$) and a trend towards a lower FVC (FVC 23.5 vs. 34.1% predicted, $p = 0.074$). There was a trend towards an older mean age at NIV initiation in the 'baseline' group compared with the 'recent' group (14.5 vs. 11.8 yrs, $p = 0.090$).

Ten of 14 children (71%) in the 'baseline' group were started on NIV for diurnal hypercapnic respiratory failure, compared with 8 of 30 (27%) in the 'recent' group ($p=0.008$). Nocturnal hypoventilation was the primary indication for starting NIV in 2 of 14 (14%) in the 'baseline' group, compared with 14 of 30 (47%) of the 'recent' group ($p=0.049$). While only 7 of 16 (44%) with the primary indication of nocturnal hypoventilation had daytime blood gas testing, most of those who did not (7 of 9 (78%)) had other evidence strongly suggesting daytime normocapnia (e.g. normal awake TcCO2, nocturnal hypoventilation present only during REM sleep, or FVC > 45% predicted). Fifteen of 16 children initiated on NIV for nocturnal hypoventilation had documented daytime symptoms attributable to nocturnal hypoventilation (morning headaches, daytime somnolence, irritability, failure to thrive, or poor sleep quality). None of the children in the 'baseline' group were started on NIV because of recurrent or severe RTIs or atelectasis (in the absence of nocturnal hypoventilation or daytime hypercapnia), but this was the primary indication for NIV initiation in 6 of 30 (20%) in the 'recent' group.

All 14 children in the 'baseline' group were started on NIV in PICU, according to hospital policy at the time, while 24 of 30 (80%) of the 'recent' group (after the change in hospital policy) were started on NIV on the respiratory medicine ward ($p < 0.0001$). For the 6 children who had NIV initiated in PICU during the recent era, the indication for PICU admission was either acute respiratory decompensation or severely symptomatic daytime hypercapnic respiratory failure. One child was admitted to the ward for elective NIV initiation but required transfer to PICU on the second day of admission after developing a lower RTI. No other adverse events were associated with NIV initiation on the ward.

Five of 14 (36%) in the 'baseline' group were started on

NIV emergently after presenting with an acute respiratory decompensation, compared with 6 of 30 (20%) in the 'recent' group (p = 0.287).

Seven of 14 (50%) in the 'baseline' group were investigated with PSG prior to initiation of NIV, compared with 21 of 30 (70%) in the 'recent' group (p = 0.313). Of the total 28 PSGs, 23 showed nocturnal hypoventilation, 1 showed significant obstructive sleep apnea (OSA) but no nocturnal hypoventilation, and 2 did not show any significant nocturnal hypoventilation or OSA. The PSG report was not available for 1 patient, and the PSG was deemed to be of inadequate duration for the remaining patient.

The average length of hospital admission for establishment of NIV (excluding those children who were initiated on NIV in the setting of an acute respiratory decompensation) was 6.9 days in the 'baseline' group and 3.5 days in the 'recent' group (p = 0.004).

DISCUSSION

This study demonstrates that the use of home NIV in children with NMD has increased markedly over a relatively short period. NIV is being introduced earlier in the course of respiratory deterioration, most often at the stage of symptomatic nocturnal hypoventilation, before the development of daytime hypercapnia. The indications for introduction of NIV have also expanded to include patients with severe or recurrent lower RTIs or atelectasis. We have shown that NIV can be safely initiated on the ward in clinically stable patients with nocturnal hypoventilation and, in this setting, hospital length of stay has reduced.

A similar increase in the use of NIV in children with NMD has been seen at other centres.45-47 This shift in practice has probably been driven by improved availability of equipment suitable for pediatric use and technical support, and an expanding evidence base showing benefits of home NIV.45-47

There are varying recommendations for the timing of NIV initiation, ranging from initiation to treat asymptomatic nocturnal hypoventilation to waiting until symptoms develop.11, 34 A complicating factor is that daytime symptoms of nocturnal hypoventilation are often only appreciated in retrospect, once they have been corrected by treatment.11, 12 At our, and other, centres, symptomatic nocturnal hypoventilation and recurrent or severe RTIs or atelectasis have become increasingly accepted indications for initiating NIV. The first of these indications is supported by the results of a small RCT, which found that at the stage of nocturnal hypoventilation with daytime normocapnia, if NIV is not introduced worsening symptoms or daytime ventilatory failure are highly likely to develop within the following 12-24 months.2 The rationale behind the introduction of nocturnal NIV for recurrent RTIs or atelectasis is that it helps to recruit lung units prone to atelectasis while the patient is asleep, which is complimentary to the goals of physiotherapy at this advanced stage of neuromuscular weakness.11 Several non-randomised studies have shown a reduction in the frequency of RTIs or hospital admissions upon starting NIV. 22, 24-28

As a result of the shift towards earlier introduction of NIV, we expected to find a reduction in the frequency of emergent NIV initiation in the 'recent' group. Our

numbers were, however, too small to determine this with statistical significance. Prevention of emergent initiation of NIV is desirable, as it would reduce distress, minimize PICU time, and allow time for patient/family education and more considered decision-making.

Recently published guidelines recommend that PSG be used to diagnose nocturnal hypoventilation and grade its severity prior to initiation of home NIV. 11, 34, 48, PSG is particularly useful to differentiate between OSA and nocturnal hypoventilation.11, 34 Unfortunately, access to specialized pediatric PSG continues to be limited in many settings. This appears to be the case at our centre, with only 64% of patients in this review undergoing PSG prior to initiating home NIV. At RCH, there is no formal sleep laboratory on-site- patients in this study were largely referred to an off-site sleep laboratory for their diagnostic and NIV follow up titration studies.

In this study, we have demonstrated that NIV can be initiated safely on the ward and not in the PICU if the patient is stable. Wherever it is initiated, it is crucial that ventilator settings and equipment are individualized by trained pediatric staff to each patient. At some centres, there is a trend towards initiating children with clinically stable conditions on NIV as an outpatient, with support provided by specialist nurse practitioners. One trial has prospectively studied outpatient NIV initiation in a population of highly selected adult patients and found equivalent outcomes in inpatient and outpatient groups.49 There are a number of

potential benefits to outpatient NIV initiation, including greater convenience for the patient and family, freeing up of inpatient beds, and overall health system cost savings.49 Before 2005, all children at our centre were initiated on NIV in the PICU. Since then, training of ward staff has allowed for clinically stable children to be initiated on the ward without any major adverse events, and the average length of hospital admission for these children has nearly halved from 6.9 to 3.5 days. Since concluding this review, we have begun to initiate highly selected children on NIV in the outpatient setting. Future studies will look at the efficacy of this intervention.

This study is limited in scope by its retrospective nature, small patient numbers and the diagnostic heterogeneity of the patients, problems that have hampered much of the research undertaken in this area. The small patient numbers made it less likely that statistically significant differences would be found between groups. Some patients did not have FVC or wake pCO2 testing as part of their workup prior to starting NIV, although six of the eight children who did not have a FVC recorded were under five years of age and were unable to reliably perform pulmonary function testing. There were only three patients for whom neither FVC nor well pCO2 results were available. In these cases, NIV was initiated either because of severe or recurrent RTIs or atelectasis, or symptomatic (PSG-confirmed) nocturnal hypoventilation.

In children with NMD, home NIV is now being initiated at an earlier stage in the progression of respiratory insufficiency, most commonly at the stage of symptomatic nocturnal hypoventilation. Furthermore, the development of recurrent or severe RTIs or atelectasis has emerged as an independent indication for NIV initiation. Further prospective multi-centre research is required to examine the potential benefits of this earlier initiation.

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