Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation

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Abstract

We reviewed the notes of 197 patients with Duchenne muscular dystrophy whose treatment was managed at the Newcastle muscle centre from 1967 to 2002, to determine whether survival has improved over the decades and whether the impact of nocturnal ventilation altered the pattern of survival. Patients were grouped according to the decade of death and whether or not they were ventilated. Kaplan Meier survival analyses showed significant decade on decade improvement in survival. Mean age of death in the 1960s was 14.4 years, whereas for those ventilated since 1990 it was 25.3 years. Cardiomyopathy significantly shortened life expectancy from 19 years to a mean age of 16.9 years.

Better coordinated care probably improved the chances of survival to 25 years from 0% in the 1960s to 4% in the 1970s and 12% in the 1980s, but the impact of nocturnal ventilation has further improved this chance to 53% for those ventilated since 1990.

Author Keywords: Duchenne muscular dystrophy; Nocturnal ventilation; Cardiomyopathy
1. Introduction

Duchenne muscular dystrophy (DMD) is an X-linked muscular dystrophy affecting one in 3500 male live births. It causes relentlessly progressive skeletal muscle wasting and, without treatment, patients rarely survive beyond their teens as the condition also causes progressive respiratory muscle weakness and respiratory failure [1]. Cardiomyopathy is responsible for the earlier death of around 10% of boys although significant cardiac changes are inevitable with increasing age [2].

Currently no treatment is available to prevent or arrest the progressive muscle weakness. Nocturnal ventilation is a treatment for respiratory failure in DMD that is not routinely offered to all patients and despite reports from USA [3] and more recently from UK [4] there still remain ethical uncertainties around the long-term benefits of this treatment for patients with advanced DMD. This may be because of perceived lack of quality of life, as well as the paucity of direct evidence of increased survival. Only four studies of neuromuscular patients on nocturnal ventilation were included in a recent Cochrane report [5], and the only randomised trial of nasal intermittent positive pressure ventilation in DMD (which used it prophylactically rather than for symptomatic patients) reported worse survival in the treated group [6].

Patients in the Northern Region of England began to be managed at a dedicated multidisciplinary clinic in the early 1970s. We have been offering ventilation to patients at the Newcastle muscle centre since 1989 although the first patients did not accept home ventilation until 1991. Since then our policy has evolved such that by the middle of the 1990s, all patients with respiratory failure were offered nocturnal ventilatory assistance.

We undertook this retrospective study to determine:

if survival has improved in DMD over the last decades, and

whether the introduction of nocturnal ventilation had altered the pattern of survival.

This has not previously been formally demonstrated in DMD, although survival data over time are available for other fatal conditions such as cystic fibrosis [7].

2. Methods

2.1. Patient group

We reviewed the notes of all patients diagnosed with DMD who were managed at the Newcastle muscle centre from 1967 to 2002. The Northern region of England has a particularly stable population that facilitates lifetime management within the same centre. We excluded seven patients who walked over the age of 13 since this is suggestive of an intermediate or Becker muscular dystrophy, and seven patients with incomplete notes who did not have routine follow-up at this centre. We documented age and cause of death and included 134 patients who died from respiratory failure who were not ventilated, 24 who were ventilated (of whom 15 are still
living), and three patients alive but not ventilated aged over 19 years. No patients had received steroid therapy. Cardiomyopathy was the cause of death in 25 patients, three however, had been ventilated so were excluded from analyses of survival in cardiomyopathy (n=22).

2.2. Indications for ventilation

Forced vital capacity (FVC) is measured at each clinic visit from the age of 7 years. Once the FVC reaches 1.25 l, serial home pulse oxymetry is performed at 3–6 monthly intervals. At each clinic appointment specific questions are asked about the number of chest infections, sleep pattern, early morning well-being, appetite and weight loss. When patients are symptomatic and/or have abnormal oxymetry in association with deteriorating FVC, they are referred to the home ventilation team. All patients used domiciliary nasal ventilators with nasal masks, nasal pillows or a combination of interfaces. Two weeks after ventilatory assistance is established home overnight oxymetry is repeated. Respiratory assessment continues at all routine follow-up appointments with the respiratory questionnaire and spirometry.

2.3. Statistical analyses

Patients were divided into groups according to the decade in which they died from the 1960s to the 1990s. In addition, age at death was compared between those patients who did and did not receive nocturnal ventilation. There were insufficient patients diagnosed with cardiomyopathy to calculate survival patterns throughout the decades. Therefore, all patients with cardiomyopathy were analysed as one group. As the data was approximately normally distributed the mean age of death from cardiomyopathy was determined. T tests were used to determine whether there were differences in the age at which walking stopped between each group.

Decade of death was chosen to differentiate between groups because (unlike cystic fibrosis where treatment begins at diagnosis) the impact of nocturnal ventilation in not seen until the terminal stage of the disease. Statistics Package for Social Sciences (SPSS) and GraphPad Prism were used to calculate survival curves (Kaplan Meier) and construct graphs for each group. All alive patients were censored on 28 February 2002.

3. Results

There were no significant differences in the mean age that walking independently became impossible between the groups. The mean age walking stopped for the whole population was 9.3 years. However, the survival curves in Fig. 1 illustrates decade-wise improvement in survival from the 1960s to date with significant differences between survival curves using the log rank test in each decade (see Fig. 1). We then compared survival since 1990 between the ventilated and non-ventilated populations (Fig. 2). Further analysis (Kaplan Meier) showed that amongst the group who did not receive ventilation and who died of respiratory failure the mean survival was 19.29 years (n=134, 95% confidence interval 18.61, 19.97) compared to a mean survival of 25.3 years for those who were ventilated (n=24, 95% confidence interval 23.11, 26.58). Fifteen ventilated patients are still alive (mean age 22.17 years, 95% confidence interval 19.78, 24.56). The presence of cardiomyopathy (n=22) significantly shortened life expectancy from 19 years to a mean age of 16.9 years (95% Confidence Interval 15.23, 17.97, t-test, P=0.0012). Further
analysis (Kaplan Meier) showed the chance of surviving to 25 years of age was 53% in the ventilated group compared with 12% for those who died in the 1980s without ventilation and 4% in the 1970s. No patient in the 1960s cohort survived beyond the age of 19.6 years (mean age of death 14.4 years, 95% confidence interval 11.9, 16.82). We also analysed the duration of ventilation. The 1-year survival of all ventilated patients was 91%, with 62% survival at 48 months and the mean duration of ventilation was 60 months (95% confidence interval 53.91, 96.91). In all patients there was complete relief of symptoms with the successful institution of nocturnal ventilation.

Fig. 1. Survival curves (Kaplan Meier), showing comparison in percentage survival decade on decade from the 1960s to 2002. The post-1990s cohort includes all boys, ventilated or not. If the ventilated group is removed from the post-1990s cohort, the 1980s and 1990s cohorts are not significantly different as shown in Fig. 2 ($P=0.82$, log rank test, data not shown). Legend: Log rank tests for successive decades 1960s vs. 1970s, $P=0.002$; 1970s vs. 1980s, $P=0.007$; 1980s vs. 1990s, $P=0.03$.

Fig. 2. Survival curves (Kaplan Meier) showing percentage survival of ventilated versus non-ventilated patients 1967–2002. (Includes live patients censored on 28th February 2002.) Legend; Log rank test for non-ventilated vs. ventilated patients post-1990 ($P=0.0001$).
4. Discussion

This is a retrospective study over a period of evolving practise, and as such has limitations. Nonetheless, the increase in life expectancy has been so striking in our ventilated group that we believe it is worth reporting. We began to offer nocturnal ventilation in the early 1990s with no systematic bias in the recruitment of patients to treatment. This is borne out by the fact that by all applicable measures, the groups of patients who did or did not accept ventilation were comparable. For example, within the ventilated and non-ventilated groups there was a similar age off feet (commonly taken as a proxy measure of severity), and in both ventilated and non-ventilated groups a wide range of IQ scores was seen. Patients with normal or above normal intelligence and those with severe or moderate learning difficulties are represented in both groups. In the ventilated group, the majority were offered ventilation following a period of monitoring and assessment, but a few were ventilated as an emergency procedure. The initial aim of ventilation was relief of symptoms and this was satisfactorily achieved; however, it became apparent that patients who used home ventilation were living longer than expected. None of our cohort of ventilated patients has had a tracheostomy, and only one has moved on to permanent 24 h ventilation (via nasal pillows); four of the rest have developed efficient glossopharyngeal breathing which maintains oxygen saturation satisfactorily during the day and these patients have had no return of the symptoms of hypoventilation. Post-prandial hypoxia has been seen in two patients relieved by use of the ventilator around meal times. After several years of nocturnal ventilation some patients experience increased fatigue during the day. This can be relieved by increasing the period of time on the ventilator either in the morning or in the evening. We have therefore, confirmed previous reports [4] that non-invasive ventilation can be regarded as a long-term treatment in this group of patients. Nine patients have died whilst using nocturnal ventilation. Three died in the first year of ventilation in the early years of the programme having never fully established regular use of the ventilator. Two had a severe co-existent cardiomyopathy, one developed severe cardiorespiratory failure, two patients died during acute chest infections: however, in one patient this followed an incident where he suffered burns and was admitted to hospital and one died following a minor surgical procedure. Six of the deaths occurred at home, two in hospital and one in a hospice.

The improvement in survival with the use of nocturnal ventilation is superimposed on a period of gradually improved survival from decade to decade. Improved organisation and delivery of care to patients with DMD probably explain the improved survival from the 1960s to the 1980s and this will inevitably have included a multitude of factors (for example systematic use of flu immunisations, increased physiotherapy input and early delivery of antibiotics). Treatment of cardiomyopathy by ACE inhibitors was not introduced until the mid-1990s. So far, numbers are small and the impact on survival is yet to be determined. Equally, over the decades, very few of the patients had had spinal surgery to enable us to analyse the impact of spinal surgery on life expectancy or its relationship to nocturnal ventilation. However, the number of patients having spinal surgery has increased over the last few years and it will be interesting in the future to evaluate the long-term outlook for patients who have had access to spinal surgery, management of cardiomyopathy and ventilation.
We have no evidence to suggest that the age or circumstances in which ventilation is introduced affects the duration or success of ventilation. Some of the early patients were ventilated following emergency admission for respiratory failure. Two such patients ventilated in 1991 and 1992 are still alive. None of our patients has been ventilated prophylactically as all patients ventilated electively have been symptomatic and have had abnormal overnight pulse oxymetry. The mean duration of ventilation in those ventilated electively is currently 35 months. As already discussed, our respiratory management policy includes regular overnight oxymetry assessments in the home once the FVC drops below 1.25 l in conjunction with in-depth questioning to elicit the onset of mild symptoms that suggest nocturnal hypoventilation. These include weight loss, daytime somnolence, frequent waking at night, chest infections and difficulty getting going in the morning after an unrefreshing sleep. The classical symptoms of hypercapnia (morning headaches and nausea) supervene after these milder symptoms, and we aim to introduce ventilation before these symptoms develop. Families prefer to prepare for nocturnal ventilation rather than be ventilated as an emergency and would like at least 6 months notice [8]. Our data (unpublished) supports this assertion and our respiratory management procedures enable discussions to begin about the impending need for nocturnal ventilation usually a year before ventilation is necessary. Formal assessment of quality of life in our patients and their carers is ongoing, but it has already been demonstrated that in DMD professionals significantly underestimate the quality of life experienced by the patient himself [9]. Technological advances made over the last decade have contributed greatly to quality of life of young men with DMD. Our unpublished data suggests that Internet access, computer games, environmental control systems, electrically operated beds and indoor–outdoor electric wheelchairs are important factors that contribute to quality of life and independence.

One of the most pressing questions in DMD is that of prognosis and survival. We present the largest retrospective review to date, which strongly supports the efficacy of nocturnal ventilation. These patients are living significantly longer over the decades from the 1960s to 2002, with the possible exception of the patients with early and severe cardiomyopathy. For the group as a whole, however, the option of nocturnal ventilation has significantly improved the chances of survival into the mid-twenties and beyond. This represents the difference between achieving an independent (though supported) life as an adult and death whilst still a child.

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References


