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Impact of invasive ventilation on survival when non-invasive ventilation is ineffective in patients with Duchenne muscular dystrophy: A prospective cohort

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ABSTRACT

Background: Many patients with DMD undergo tracheostomy. Tracheostomy is associated with certain complications, however its effect on prognosis is not known.
Methods: The relationship between type of mechanical ventilation and survival at 12 years was evaluated in a prospective cohort of patients with Duchenne muscular dystrophy followed in a French reference center for Neuromuscular Diseases. Cox proportional-hazards regressions were used to estimate the hazard ratios associated with risk of switching from non-invasive to invasive ventilation, and with risk of death.
Results: One hundred and fifty patients were included. Initial use of invasive ventilation was associated with an episode of acute respiratory failure ($p < 0.0001$) and with a severe clinical status ($p < 0.05$). Risk of death was associated with swallowing disorders (2.51, IC [1.12–5.66], $p < 0.03$) and cardiac failure ($p < 0.05$) but not with type of mechanical ventilation.
Conclusion: Switching to invasive ventilation is appropriate when non-invasive ventilation is ineffective.

1. Introduction

Duchenne muscular dystrophy (DMD) is a severe hereditary myopathy caused by mutation of the DMD gene, which is located on the X chromosome (at. Xp21.2). This gene encodes a protein called dystrophin [1].

DMD is the most common myopathy in children, affecting 1 in every 3500 male births [2]. In 2009, the overall prevalence of patients with DMD with a confirmed genetic diagnosis reached 3.9 per 100,000 inhabitants in France [3]. DMD is characterized by a loss of integrity of the muscle cell membrane, followed by degeneration of muscle tissue due to a lack of dystrophin [4].

The main cause of death is heart failure [5], however, if ventilatory assistance is not provided, progressive weakness of the respiratory muscles also leads to early death [6]. The life expectancy of patients has doubled (from 15 to 30 years) since the introduction of mechanical ventilation (MV) and cardiac care in the 1960s [7–11].

MV is indicated when vital capacity drops below 20% of the theoretical value, or $PaCO_2$ level is above or equal to 45 mmHg [6,12]. Noninvasive ventilation is usually initiated nocturnally to treat sleep-related breathing disorders and hypoventilation, which are frequent in these patients [13].

Currently, mechanical ventilation is usually initiated with noninvasive ventilation. Since methods of noninvasive ventilation and interfaces such as mouthpieces have improved, NIV can now be extended to daytime for patients who are completely dependent on mechanical ventilation with systematic cough assistance [11,14,15]. However, when non-invasive ventilation becomes ineffective or poorly tolerated due to severe bulbar dysfunction, or because the

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Abbreviation list

BMI	body mass index
CO_2	carbon dioxide in arterial blood
DMD	Duchenne muscular dystrophy
FiO_2	Fraction of inspired oxygen
IV	invasive ventilation
IC	interval of confidence
HR	Hazard ratios
LVEF	left ventricular ejection fraction
MV	mechanical ventilation
MmHg	millimeters of mercury
Mmol/l	millimol per liter
NIV	non-invasive ventilation
OR	Odds Ratio
$PaCO_2$	arterial pressure of carbon dioxide
PH	potential of hydrogen
PaO_2	oxygen tension in arterial blood
VC	vital capacity

cough assistance is insufficient and the patient requires frequent tracheal aspiration through tracheotomy, it is necessary to switch to invasive ventilation [6,16,17].

Tracheostomy is associated with certain complications such as stomal hemorrhage and infection, or tracheal stenosis [18]. However, it is not known if tracheostomy is associated with a worse prognosis in patients with DMD.

The aim of this prospective cohort study of patients with Duchenne muscular dystrophy, who switched to IV because NIV was ineffective or not tolerated, was to assess the relationship between the method of MV and survival at 12 years.

2. Population and methods

2.1. Study design and setting

We conducted a prospective observational cohort study of patients followed-up in the MV department of Raymond Poincaré Hospital, one of 14 reference centers for neuromuscular diseases in France, between January 1997 and September 2015.

2.2. Population

Male patients with Duchenne muscular dystrophy for whom home mechanical ventilation had been initiated for at least 6 h per day between 1997 and 2014, were eligible for this study.

2.3. Data collection

Data were collected at initiation of MV and during annual follow-up visits, until the twelfth year after initiation, death or loss to follow-up. Baseline characteristics were recorded, including age at diagnosis, height, weight, age at initiation of MV and respiratory status ($PaCO_2$, PaO_2, pH, Total CO_2, vital capacity). The following criteria for NIV initiation were also recorded: clinical signs suggestive of hypercapnia (dyspnea at rest and on exertion i.e dyspnea when speaking, eating or simply sitting in the wheelchair, morning headaches, orthopnea, sleep disturbances, diurnal sleepiness), alveolar hypoventilation ($PaCO_2 \geq 45$ mmHg), nocturnal arterial oxygen desaturation ($SaO_2 \leq 88\%$ for five consecutive minutes) and restrictive lung disease (vital capacity below 20% of predicted capacity) [6,12]. In addition, the following variables were recorded: functional autonomy, mode, type of MV and interface, and prescribed ventilation time. Finally, two other typical complications of DMD were recorded: swallowing disorders and cardiac disorders. Left Ventricular Ejection Fraction (LVEF) was classified in four levels: normal (≥55%) mild (45–54%), moderate (30–44%) and severe (<30%) [19].

During each follow-up visit, the following data were recorded: blood gases (during free breathing at least 2 h after disconnection), fraction of inspired oxygen, vital capacity (VC), prescribed ventilation time and left ventricular ejection fraction. Assessments were carried out when the patients were stable (i.e. not during an acute episode of respiratory failure).

2.4. Statistical analysis

Descriptive statistics are presented as counts and percentages, or means and standard deviations, with skewed continuous data summarized as medians and interquartile ranges.

Patients were grouped according to the type of ventilation used at initiation of MV, and compared. A student test (equal variance) or Welch–Satterthwaite *t*-test (unequal variance) was used to analyze quantitative variables, a Mantel-Haenszel Chi-Square test was used to analyze qualitative variables and Fisher's exact test was used when the sample sizes were small (<5).

Survival was calculated from the date of initial ventilation to the date of death from any cause. A Cox proportional-hazards model was used to estimate hazard ratios (HR) for death associated with both types of MV, after adjustment for risk factors. Covariates included were age at diagnosis, age at onset of MV, and variables which had a p-value below 0.25 in the univariate analysis, identified by stepwise forward selection. Kaplan–Meier curves and adjusted survival curves with a Cox regression model were plotted to assess survival time as a function of type of ventilation.

Statistical significance was set at 0.05 (two-tailed test). All statistical calculations were performed using SAS 9.3 software for Windows, and R software version 2.2.0.

Patients were informed about the study and could oppose the use of their data. The study was performed in accordance with ethical and regulatory standards for clinical research.

3. Results

3.1. Characteristics of the population (Table 1)

Between 1997 and 2014, 150 patients were included in the cohort (Table 1). Mean age at the time of diagnosis was 5.6 (±3.9) years. At initiation of ventilation, 96 (64%) patients were underweight (BMI < 18.5). All used an electric wheelchair. One hundred and forty-four (96%) patients could get out of their homes using a powered wheelchair and 6 (4%) were confined to bed. One hundred and twenty-eight (82%) patients had cardiac disorders, of whom 64 (50%) had left ventricular dysfunction with a mean LVEF of 43.5% (±8.2), and 16 (11%) had swallowing disorders. 25% of the patients had orthopnea and 48 (32%) had exertional dyspnea.

The respiratory status of patients, who initiated MV with IV, because they did not tolerate NIV, was significantly more severe than that of patients on NIV. One hundred percent of patients on IV had orthopnea compared with 20% of patients on NIV ($p < 0.0001$). Dyspnea at rest (45% vs 16%, $p < 0.05$) and exertional dyspnea (55% vs 26%, $p < 0.05$) were also significantly more prevalent in patients on IV.