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# Managing Duchenne muscular dystrophy – The additive effect of spinal surgery and home nocturnal ventilation in improving survival

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## Abstract

**Objectives:** To determine the long term survival in patients with Duchenne muscular dystrophy (DMD) following spinal surgery and nocturnal ventilation.

**Study design:** A retrospective review of 100 consecutive patients born between 1970 and 1990 was conducted.

**Results:** Forty-seven patients had surgical spinal fusion, 27 were subsequently ventilated. Fourteen patients received ventilation only. Thirty-nine patients received neither intervention. The age at which ventilation was required correlated with the age at which ambulation was lost. Those who walked for longer were less likely to require spinal surgery. Mean vital capacity dropped from 1.4 to 1.13 L 1 year post-operatively. Patients having both spinal surgery and ventilation had a median survival of 30 years whereas those who were only ventilated survived to 22.2 years.

**Conclusion:** Nocturnal ventilation improves survival in DMD. Spinal surgery does not increase forced vital capacity but in combination with nocturnal ventilation further improves median survival to 30 years.

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**Keywords:** Duchenne muscular dystrophy; Scoliosis; Spinal surgery; Nocturnal ventilation; Survival

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## 1. Introduction

Duchenne muscular dystrophy (DMD) is an X – linked muscular dystrophy affecting 1 in 3500 male live births, causing progressive weakness of skeletal, respiratory and cardiac muscles due to the absence of dystrophin in the subsarcolemmal cytoskeleton [1]. Without intervention, the progression of the disease

causes loss of independent ambulation by the age of 13 years, followed by the development of scoliosis, respiratory failure and cardiomyopathy, with a mean age of death of 19 years. Proactive management of these complications leads to improvements in quality of life and survival, but there are few data showing the additive effects of different interventions.

The aims of the present study were to review the outcome of spinal stabilisation in children with DMD (none of whom had been treated with corticosteroids) with respect to FVC, and to determine the survival of patients who had undergone spinal surgery and were subsequently ventilated nocturnally in comparison to those who had neither intervention.

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## 2. Patients and methods

The study cohort included 100 patients with DMD born between 1970 and 1990 followed up at the Newcastle Muscle Centre. Ninety-three patients had a confirmed molecular diagnosis. Seven were diagnosed by absence of dystrophin on biopsy or the biopsy of an affected family member. Several patients had retrospective molecular diagnoses made in the years after they died. Patients who walked over the age of 13 years were excluded as they may have had a milder intermediate or Becker type of muscular dystrophy. Patients who were not followed up long term at the Newcastle Muscle Centre were also excluded. Use of aids to prolong walking was noted but the age at loss of the ability to walk independently was documented for analysis. The four teams integrally involved in the management of this group of patients (cardiology, respiratory, surgical and the Newcastle Muscle Clinic) have been led by the same people for 18 years enabling stable and standardised care to be delivered. Protocols for spinal surgery, ventilation and cardiac management have all been developed according to the growing knowledge in this field over the period under study. Respiratory surveillance consisted of measurement of forced vital capacity at six monthly intervals, supplemented by symptom enquiry and home overnight pulse oxymetry once the FVC fell to less than 1.25 L. The indication for ventilation was the development of symptomatic nocturnal hypoventilation or a forced vital capacity less than 0.6 L [2]. This policy was followed from the early 1990s.

Patients were referred for spinal surgery evaluation following the development of a postural scoliosis and surgery was offered if the curve was progressive over a period of six months or the Cobb angle was more than 20°. Surgery became more accepted by patients and their families over the early 1990s.

Prior to the 1990s cardiomyopathy was noted clinically, usually by the presence of clinical signs of cardiac failure whereas the clinic now has a policy of therapeutic intervention based on routine echocardiographic evaluation which is conducted annually from the age of 10 years [3]. The group of patients reported here include those who were managed before systematic guidelines were introduced as well as the more recent patients who have been followed according to protocol. However, all patients received the same baseline standards of care from the Newcastle Muscle Centre which did not change during the period under study [4].

## 3. Statistical methods

Kaplan–Meier survival analyses were conducted to determine survival patterns. Median survival was calculated as the time at which half of the subjects had

died. Censored subjects included all alive patients and there were no patients lost to follow up. The logrank test was applied to the Kaplan–Meier analysis on all patients born between 1970 and 1990 including those who did not have spinal surgery. Cox regression analysis was carried out using the categorical variables relating to the spinal surgery, cardiomyopathy and ventilation together with the age at which the patient could no longer walk. The analysis was carried out using a variable selection process to determine the variables on which survival depended. Pearson correlation calculations were used to analyse the correlation between age at death or age at ventilation and loss of ambulation.

## 4. Results

One hundred consecutive patients were included, 47 patients had had spinal surgery including 27 who had had spinal surgery and subsequent nocturnal ventilation. Fourteen patients did not have spinal surgery but had received nocturnal ventilation and 39 patients had neither intervention. Five patients had severe cardiomyopathy and were refused surgery. To ensure that these patients did not confound survival statistics in the non-operated groups they were excluded from survival analysis. Consequently, survival analyses were carried out on 27 patients in the surgery and ventilation group (22 censored), 13 patients in the ventilation only group (3 censored) and 35 in the no intervention group (2 censored). The group of boys who have had spinal surgery only are currently too young for meaningful survival analysis: as these patients are under the mean age for ventilation they may well in the future receive both interventions. The mean age at loss of ambulation for all patients was 9.42 years and there was no significant difference between the groups. Mean age at surgery was 14 years. Ventilation was introduced at 17.4 years in the group who had spinal surgery and 18.2 years in the group who did not have spinal surgery. This was not statistically significantly different. After 1990 all spinal fusions were performed by the same surgeon, who used the universal stratec system ( $n = 41$ ). Operative information on the remaining six patients was incomplete. As illustrated in

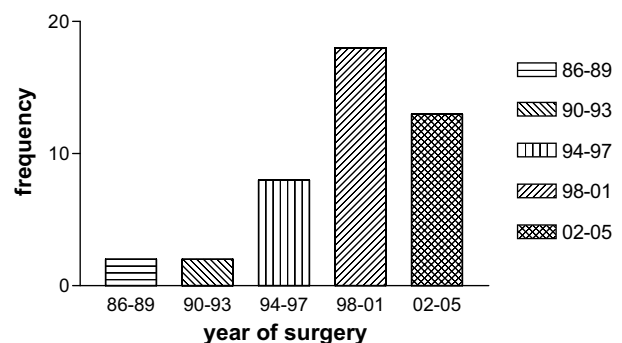


Fig. 1. Number of spinal fixations performed between 1986 and 2005.

Fig. 1, there have been an increasing number of patients having spinal surgery over the years. This is explained in part by a greater acceptance of the procedure amongst the patients and their families and partly to a more systematic policy of offering surgery to boys with progressive scoliosis [5].

There were no peri-operative deaths following spinal surgery. Complications were rare. Two patients had gastrointestinal bleeding associated with non-steroidal anti-inflammatory therapy. One patient had post-operative ileus. Eighteen months after surgery, one patient developed a spinal infection which resolved when the surgical rods were removed. One patient developed a pressure sore which was successfully treated with dressings. Two particularly thin patients had chronic pain due to the prominence of metal prostheses. There were no neurological complications. Functional problems such as difficulty feeding were noted in eight patients immediately post-operatively. In the long term, none of the patients have become bed bound due to their posture or positioning but three developed neck contractures resulting in a side flexed posture, one severe. All three patients now use collars to support the neck in a comfortable and functional position.

The number of boys assessed as not requiring surgery (i.e. without a progressive scoliosis) has remained stable over time and strongly correlates with the age at loss of independent ambulation. Seven out of 14 boys who lost ambulation aged 11–12 years did not develop a progressive scoliosis and 7 did. This suggests that boys who walk longer are at a lower risk of developing a scoliosis. The age at which loss of ambulation occurred also correlated strongly with the age at which ventilation was instituted,  $p = 0.01$  Pearson's  $r$ , 0.588 and less so but still significantly, with the age of death,  $p = 0.02$  Pearson's  $r$ , 0.196 (Fig. 2a and b).

The effect of spinal surgery on respiratory function is controversial. Our data confirm that spinal surgery does not improve forced vital capacity (FVC). Mean FVC reduced significantly from immediately prior to surgery to 1 year after surgery, 1.4 L (95% Confidence interval 1.21–1.61) versus 1.13 L 95% (confidence interval 0.891–1.371)  $p = 0.0006$  (Fig. 4).

The median survival of patients who had had spinal surgery and subsequently received nocturnal ventilation was 30.0 years compared to 22.2 years for those who were ventilated but did not have spinal surgery (Fig. 3). The percentage chance of survival to 24 years of age was 84% in those who had both ventilation and spinal surgery ( $n = 27$ ), 34.6% in those who only had ventilation ( $n = 13$ ) and 10.7% in those who received neither intervention ( $n = 35$ ) (Table 1). Cox regression analysis using the categorical variables relating to spinal surgery, cardiomyopathy and ventilation together with the age at which the patient could no longer walk shows that there are significant differences in survival for patients undergoing

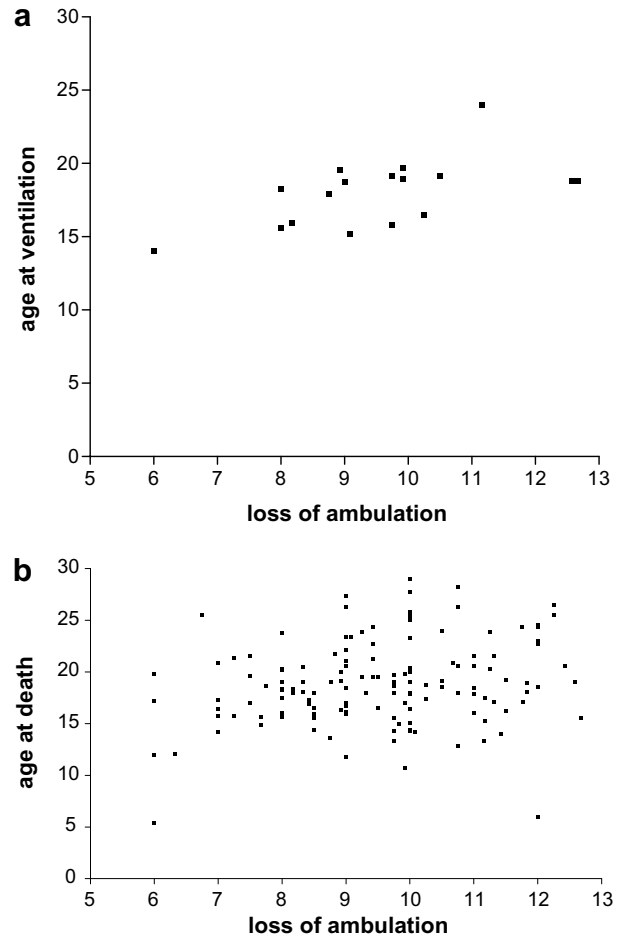


Fig. 2. (a) Correlation between loss of ambulation and age at ventilation. (b) Correlation between loss of ambulation and age at death.

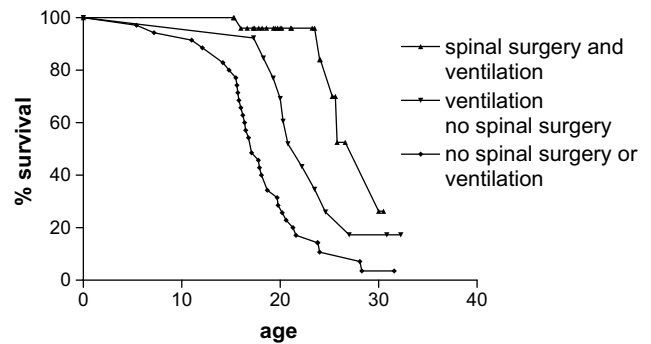


Fig. 3. Kaplan–Meier survival plot to show the impact of spinal surgery and ventilation on survival. Survival curves are significantly different  $p = 0.0001$ .

spinal surgery and also between the different treatments received. (Table 2). The 3 boys who have survived over the age of 21 years without these interventions all walked until they were 11–12 years of age.

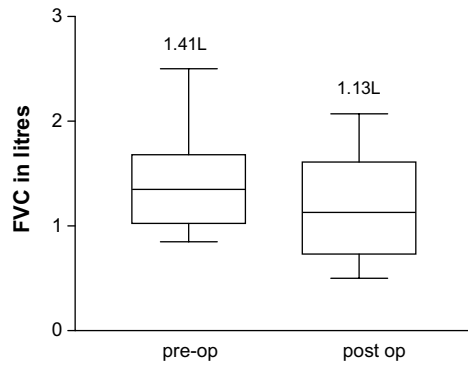


Fig. 4. Forced vital capacity at the time of spinal surgery and 1 year later.

Table 1  
Age at loss of ambulation and percentage survival

	Group 1 (N = 27)	Group 2 (N = 13)	Group 3 (N = 35)
Age at loss of ambulation	9.6	8.9	8.9
Mean age ventilated	17.4	18.2	N/A
Median age of survival	30	22.2	17.1
% chance of survival to 20 years	96	69.2	25.7
% chance of survival to 24 years	84	34.6	10.7
% chance of survival to 32 years	26.5	17.3	3.57

Group 1 Patients with spinal fixation and ventilation.

Group 2 Patients with ventilation only.

Group 3 Patients with neither spinal surgery nor ventilation.

Table 2  
Cox regression analysis of the categorical variables relating to spinal surgery, cardiomyopathy, ventilation and age loss of independent ambulation

Variables included	Regression coefficient	Significance probability	Hazard ratio
Ventilation	1.382	<0.0005	3.984
Age off feet	-0.312	<0.0005	0.732
Spinal surgery	1.068	0.006	2.910

Apart from patient and family preference, the major medical reason for children not to be offered surgery is the presence of progressive non-responsive cardiomyopathy, which is now aggressively sought pre-operatively. An ejection fraction of below 60% if accompanied by abnormal segmental wall motion is considered abnormal. Cardiomyopathy is a major cause of death in DMD, so we attempted to elucidate the presence of cardiomyopathy in the different groups to see if this contributed to the different survival rates. Of 39 patients who did not have spinal surgery, about 25% were diagnosed with cardiomyopathy. This includes the five patients who were refused surgery because of the presence of very early cardiomyopathy. Eleven patients to date out of the 47 who did receive spinal surgery have

developed cardiomyopathy since having surgery, 2 of whom died of cardiac failure aged 16.3 and 16.5 years. The remaining 9 are alive, maintained on combination therapy of ACE inhibitors and beta-blockers. All are also ventilated and their median age is 20.2 years.

Determining cause of death is difficult as patients often die at home and the majority do not have a post mortem, those who have undergone post mortem usually show features of cardiac involvement even if the cause of death appeared to be respiratory. We have attempted to determine cause of death where possible. Five patients died in the group who were ventilated and had spinal surgery. Three had respiratory infections in the days preceding their death, one died suddenly after momentarily feeling unwell and the other was generally unwell for a few weeks before dying. In the group who had spinal surgery and were not ventilated there were 6 deaths, three presumed cardiac and three respiratory. Ten boys died who were ventilated and did not have spinal surgery. One died following a local anaesthetic, one aspirated following a minor procedure, both were well prior to their death, another developed a chest infection following a burn, two died suddenly, presumably from cardiac causes, another had a progressive severe cardiomyopathy, two did not effectively establish ventilation and died during respiratory infections. In two cases there was no obvious cause of death but both young men were unable to maintain effective oxygen saturation over a few days before they died.

It was even more difficult to determine cause of death in the group of boys who did not have spinal surgery or ventilation. Some died before sufficiently accurate records were kept but about 25% had a progressive, severe cardiomyopathy and the others mainly died as a result of respiratory failure or infection.

## 5. Discussion

This report demonstrates the benefits of systematic assessment and adhering to management protocols which enable timely interventions in managing DMD patients with a clear improvement in survival over the decades [6]. We and others have already reported that the use of home nocturnal ventilation improves life expectancy and quality of life in DMD. Our current results suggest that the combination of spinal correction and the provision of home nocturnal ventilation have an additive effect on survival for boys with DMD with a progressive scoliosis and respiratory failure but without severe progressive cardiomyopathy. The two interventions together enhance longevity greater than one alone. Spinal surgery in this group is well tolerated: there were no peri-operative deaths in our cohort and few complications.

In keeping with previous reports [7], around 10% of our DMD cohort did not develop progressive scoliosis,

and some of these had relatively milder disease demonstrated by their continued ability to walk beyond the age of 11 (but less than 13 years). Routine daily use of daily corticosteroids in ambulant boys with DMD has now been consistently reported to result in a prolongation of ambulation and a reduction in the need for scoliosis surgery, though some may experience intolerable side effects such as weight gain or behavioural problems. For the majority of steroid treated boys however, the effects on ambulation and scoliosis accompanied by the increase in FVC and the potential protective effect on cardiac function imply that a further increase in survival can be anticipated.

The FVC dropped significantly in the year following surgery, and then continued to decline following the predictable pattern seen in the teenage years in DMD. It has been suggested previously that spinal surgery stabilises the FVC following surgery [8,9], however other authors have reached similar conclusions to our data [10]. Despite the fall in FVC, we did not notice any obvious increase in respiratory problems in patients who had spinal surgery and it is interesting to note the significantly increased survival in the group of patients who have both spinal surgery and ventilation. Spinal surgery offers a more comfortable and cosmetic sitting position and none of the subjects receiving spinal surgery have become bed bound as a result of their muscular dystrophy. Miller [11] in a group of patients treated before nocturnal ventilation was used in DMD noted that the age of death was the same (18.3 years) whether patients had spinal surgery or not. Our data confirm our previous finding that improvement in survival in DMD is dependent on nocturnal ventilation, with the combination of spinal surgery and ventilation improving survival further. We have previously noted survival of ventilated patients to be almost 25 years of age (including patients who had and had not spinal surgery) [6].

The group of patients who were ventilated but did not have spinal surgery reflects the fact that at the time when spinal surgery would have been appropriate (i.e. 3–4 years before ventilation was introduced) it was not systematically offered, and very few families accepted it. A closer examination of the cause of death in this group reveals three untimely deaths and two who did not effectively use ventilation which may have contributed to the younger age at death seen in this group of patients. It is also possible that over the decade management of respiratory complications in ventilated patients has improved. However, the use of the cough assist machine (available for use in the UK since 2004) and breath stacking resuscitation bag have been more recently incorporated into our management policies and do not yet have an impact on these survival data. Due to systematic serial evaluations of respiratory function since the early 1990s very few patients now are ventilated as an emergency and most are seen as out-patients.

The one variable which it is difficult to control for is cardiomyopathy and the effect of its treatment. It is difficult to compare the incidence of cardiomyopathy in the 1980s to that seen today. In the earlier years only symptomatic patients were assessed whereas today all patients are routinely evaluated from the age of 10 or before any surgical procedure according to ENMC guidelines [9]. In Newcastle, patients with cardiomyopathy are nowadays treated with a combination therapy of ACE inhibitors and beta-blockers. [3]. There is therefore a lower threshold both for diagnosis and treatment of cardiomyopathy. However, all patients referred for spinal surgery were preoperatively screened for the presence of cardiomyopathy and it could have been possible that a contributor to the lower rates of survival within the non-operated group was a higher incidence of early and more severe cardiomyopathy. We therefore excluded from survival analyses patients who were refused spinal surgery on these grounds, and it is these data which are presented. For the future, it will be of interest to see if the accepted trend towards earlier detection and treatment of subtle cardiomyopathy has a further positive impact on survival. Systematic assessment will also allow better quantification of the scale of this problem in the future.

Survival is clearly influenced by a number of factors. Our previous publication of progressive improvement in survival over the decades probably related to better management including use of antibiotics for pneumonia and chest infections during the 70s and 80s and the impact of ventilation in the 1990s [6]. In that report it was not possible to evaluate the effect of spinal surgery. However, we now demonstrate that the cumulative effect of spinal surgery and ventilation further improves survival. Walking longer (over the age of 11) is not a guarantee of greater survival but the age at loss of ambulation is an important predictor of prognosis and strongly correlates with the age at which ventilation is required. Loss of ambulation correlates more closely with age at ventilation than with age at death suggesting a close correlation between respiratory and skeletal muscle strength, but not, as previously reported, between skeletal muscle strength and cardiac function. Corticosteroids improve muscle strength and prolong ambulation but it is too early to tell whether this intervention will impact on survival in turn.

## 6. Conclusion

In our cohort of patients who developed respiratory insufficiency in the years after spinal surgery, nocturnal ventilation is a very successful treatment which prolongs life up to a median age of 30 years. Age at ventilation and whether or not spinal surgery is required correlates with age at loss of ambulation so those boys who walk for longer are ventilated a later age and are less likely

to require spinal surgery. Nocturnal ventilation is offered routinely in the Newcastle Muscle Centre through the North East Assisted Ventilation Service and the mean age at ventilation for all patients is 17.74 years. Spinal surgery is routinely offered to patients with a progressive scoliosis and mean age at surgery is 14 years of age. Because of the staggered nature of the interventions and the gradual acceptance of both ventilation and spinal surgery we have a mixed patient population, some of whom have accepted both treatments whereas others have ‘missed the boat’ for surgery or refused. While it is difficult to determine precisely the relative impact of spinal surgery and ventilation in a retrospective study such as this, it is clear that a collaborative and proactive approach to management offers the best chance of improving survival.

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