

Survival of Patients With Spinal Muscular Atrophy Type 1

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KEY WORDS

home mechanical ventilation, mechanical assisted cough, pediatric palliative care, spinal muscular atrophy type 1, long survival

ABBREVIATIONS

CI—confidence interval
 MAC—mechanically assisted coughing
 NIV—noninvasive bilevel ventilation
 NRA—noninvasive respiratory aid
 NT—no treatment
 SMA—spinal muscular atrophy
 SMA1—spinal muscular atrophy type 1
 SpO₂—pulse oxygen saturation
 TV—tracheostomy and invasive mechanical ventilation

Dr Cutrera conceptualized and designed the study, critically reviewed the manuscript, and approved the final manuscript as submitted; Dr Ottonello designed the data collection instruments, carried out the initial analyses, designed the study, and drafted the initial manuscript; Drs Chiarini Testa and Bignamini coordinated and supervised data collection and reviewed and revised the manuscript; Dr Ravà carried out the initial statistical analysis; Ms Mastella coordinated and supervised data collection; Dr Veljkovic critically reviewed the manuscript and made substantial contributions to the statistical analysis; and Dr Gregoretti conceptualized and designed the study, drafted the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Survival of children with spinal muscular atrophy type 1 is determined by treatment choice: tracheostomy with mechanical ventilation, noninvasive mechanical ventilation, or a palliative approach. Few data are available on life expectancies with different approaches.



WHAT THIS STUDY ADDS: The present study provides data comparing therapeutic strategies that affect life expectancy. Clinicians involved in the care of patients with spinal muscular atrophy type 1 should be aware of survival trends while awaiting more definitive therapeutic strategies.

abstract

BACKGROUND: Spinal muscular atrophy type 1 (SMA1) is a progressive disease and is usually fatal in the first year of life.

METHODS: A retrospective chart review was performed of SMA1 patients and their outcomes according to the following choices: letting nature take its course (NT); tracheostomy and invasive mechanical ventilation (TV); continuous noninvasive respiratory muscle aid (NRA), including noninvasive ventilation; and mechanically assisted cough.

RESULTS: Of 194 consecutively referred patients enrolled in this study (103 males, 91 females), NT, TV, and NRA were chosen for 121 (62.3%), 42 (21.7%), and 31 (16%) patients, respectively. Survival at ages 24 and 48 months was higher in TV than NRA users: 95% (95% confidence interval: 81.8%–98.8%) and 67.7% (95% confidence interval: 46.7%–82%) at age 24 months ($P < .001$) and 89.43% and 45% at age 48 months in the TV and NRA groups, respectively ($P < .001$). The choice of TV decreased from 50% (1992–1998) to 12.7% (2005–2010) ($P < .005$) with a nonstatistically significant increase for NT from 50% to 65%. The choice of NRA increased from 8.1% (1999–2004) to 22.7% (2005–2010) ($P < .001$).

CONCLUSIONS: Long-term survival outcome is determined by the choice of the treatment. NRA and TV can prolong survival, with NRA showing a lower survival probability at ages 24 and 48 months. *Pediatrics* 2013;131:e1509–e1514

Spinal muscular atrophy (SMA) type 1 (SMA1; Werdnig-Hoffmann disease) is the second most common, potentially lethal autosomal recessive disorder, affecting 1 of 6 to 8 live births and has a 1 in 34 asymptomatic carrier frequency.^{1,2} SMA ranges in severity from severe weakness and definitive need for ventilatory support as newborns to muscle weakness first seen in adulthood. Patients with SMA type 3 develop the ability to walk independently for some period of time. Patients with SMA type 2 never walk but are able to sit independently for some period of time. Children with SMA1 can never roll, sit, or walk. SMA1 is a progressive disease³⁻⁵ and is usually fatal in infancy.^{6,7} SMA1 can be additionally subdivided by severity according to the age at first manifestation of clinical symptoms.⁸ It can be defined as “true” when the onset of clinical symptoms is before 3 months of age with the inability to raise the head and as “intermediate” when the onset of symptoms is after 3 months of age with the ability to raise the head. The condition’s severity can be ranked as “severe 1A”, “typical 1A,” or “mild 1B”, according to the age at first episode of respiratory decompensation. In the most severe phenotype, 24 hours of mechanical ventilation per day are needed before 6 months of age.⁹⁻¹¹ New management approaches have already been described in SMA1, with children becoming dependent on continuous noninvasive respiratory aid.^{9,12,13} Its aim was to provide periods of rest for inspiratory muscles, to promote lung growth, and to prevent pectus excavatum¹⁴ to maximize cough flows and maintain normal alveolar ventilation¹¹. In addition, it can be used in the postextubation period when patients are recovering from an acute episode of respiratory failure requiring airway intubation^{15,16}. “Symptomatic treatment” as well as low pressure values of bilevel ventilation are inadequate for advanced patients.¹⁷

The purpose of this study was to describe the outcome according to the choice of treatment and changes in the SMA patient’s life and to compare these findings with previously reported survival patterns.

METHODS

The medical records of all patients affected by SMA1, followed up by 4 Italian centers from October 1, 1992, to December 31, 2010, were reviewed. The diagnoses were made during the early 1990s by clinical and electrophysiologic study and, as early as it was available, by genetic study. The severity of the patients’ phenotypes was classified for all patients according to age at first clinical symptoms⁸ and, for the mechanically ventilated patients only, to age at first respiratory decompensation.¹³ The study was approved by local ethical committee at Bambino Gesù Children’s Hospital, as a survey of Sma type 1 children.

The exclusion criterion was diagnoses performed after the ninth months of age, because older children could have been able to sit and so may not have had SMA1. Data pertaining to relevant variables were obtained from medical records or from an online service. They included date of birth, age at first clinical symptoms, choice of treatment, and date of death, if applicable. Age at first respiratory decompensation was obtained only for the mechanically ventilated patients.

Parents were given the following choices: (1) to “let nature take its course,” meaning to provide supportive care only (no treatment [NT]); (2) to perform elective tracheostomy and invasive mechanical ventilation (TV); and (3) only from January 1999 to use noninvasive respiratory aid (NRA). NRA consisted of noninvasive bilevel ventilation (NIV) and mechanically assisted coughing (MAC). Invasive ventilation, MAC, and NIV were applied as previously described.^{9-12,15-21} Equipment

at home consisted of 2 mechanical ventilators, 2 vacuum-operated machines for aspirating oral and bronchial secretions, 1 MAC machine functioning both in manual and in automatic mode, 1 pulse oximeter, 1 active humidifier for mechanical ventilation, and 1 manual resuscitator bag.

Parents choosing long-term ventilation were instructed in the hospital setting in basic life support and in treating respiratory decompensation. After 2002 we adopted the protocol published by Gomez-Merino and Bach²⁰ for the use of respiratory muscle aid by using oximetry feedback.

During acute episodes of acute respiratory decompensation, peripheral hemoglobin pulse oxygen saturation (Sp_{o2}) was continuously monitored. Aggressive MAC, postural drainage, and deep airway suctioning were used when Sp_{o2} fell below 95%. Broad-spectrum antibiotics were prescribed. Parents were allowed to increase NIV peak pressure up to 25 cm H₂O in the presence of desaturation, to increase the back-up ventilator rate to avoid patient-ventilator asynchrony, and to use MAC until Sp_{o2} normalized. Parents could also increase insufflator-exsufflator pressures as previously described.¹² Patients who needed intubation for acute respiratory failure were extubated to NIV/MAC to their premorbid settings according to an already described extubation protocol.⁹ Atropine was administered to reduce oropharyngeal secretions. Supplemental oxygen was usually avoided at home. Parents were advised to use it during secretion mobilization and periods of respiratory arrest.¹²

All patients were surveyed for the occurrence of respiratory tract infections causing desaturation, continuous application of NIV, and need for hospital admission. Respiratory tract infections were defined by the presence of fever and mucopurulent sputum with an Sp_{o2}

<95%. Other respiratory complications such as pneumothorax and pneumomediastinum were taken into account.²² Acute episodes of respiratory decompensation were indicated by worsening of paradoxical breathing and episodes of transcutaneous SpO₂ <95% lasting several minutes with the need for continuous NIV to avoid respiratory distress and desaturation.¹³ Respiratory arrest was defined by apnea and desaturation <40% reversed only by basic life support.²³ Avoided hospitalization was defined by management of the patient's desaturations at home with a continuous application of NIV and frequent use of MAC.¹⁶ Acute respiratory failure in the hospital setting was defined by respiratory distress, tachypnea, and severe gas-exchange derangement. Hypoxemia was defined by SpO₂ <95% despite an oxygen inspired fraction >0.5. Respiratory acidosis was defined as an increase in PaCO₂ causing a pH <7.35.

Statistical Analysis

Categorical variables were compared through χ^2 or Fisher's exact test when appropriate. Continuous variables were represented by means and SD or medians and range, and analyzed by *t* test and analysis of variance or Mann-Whitney and Friedman tests as needed. The survival experience of patients was analyzed by using the Kaplan-Meier method. A comparison of the survival curve estimates for each of the 3 groups of patients (NT, NRA, TV) was made by log-rank test. SMA severity according to the age at first respiratory decompensation between the NRA and TV groups was compared by Fisher's exact test. The χ^2 for trend test was used to evaluate the trend

of proportions over time. Statistical analysis was performed by using Stata, version 11.2 (StataCorp LP, College Station, TX).

RESULTS

Of 219 patients initially analyzed, 14 were excluded because of late and inadequate diagnoses and 11 patients were excluded due to incomplete data. One hundred ninety-four patients who satisfied the criteria for SMA1 diagnosis were considered eligible. All patients were discharged from the hospital. Parents were trained for a predefined period at a training center. This center was also in charge of setting up the home care program.

NT was used in 121 patients (62.3%) (70 males and 51 females), TV in 42 patients (21.7%) (19 males and 23 females), and NRA in 31 patients (16%) (14 males and 17 females). Table 1 shows the classification of SMA severity according to the age at onset of clinical symptoms.⁹ No differences between the 4 hospitals could be found.

The proportion of patients with "true" SMA1 was higher in the NT group compared with NRA and TV (NT versus NRA, $P < .01$; NT versus TV, $P < .01$). No significant difference regarding the proportion of "true" and "intermediate" SMA1 was found between NRA and TV groups.

Table 2 shows the classification of SMA severity according to age at first respiratory decompensation.¹⁷ The mean age at first respiratory decompensation was 6.9 ± 4.3 and 12.6 ± 14.4 months in the TV and NRA groups, respectively ($P = .004$). One patient in the NRA group needed mechanical ventilation from birth, and 1 patient needed mechanical ventilation at the age of 42 months.

Interestingly, 6 patients in the NRA group (19.3%) did not show any episode of respiratory decompensation and avoided hospitalization at the mean age of 47.1 ± 21.1 months (range: 16–78 months). When SMA1 severity was ranked in ventilated patients according to age at the first respiratory decompensation,¹⁷ the proportion of typical SMA1 with first respiratory decompensation between 4 and 18 months of age was higher in the TV group compared with NRA group ($P = .014$).

When patients were considered over a 6-year time period, the number and percentage of patients assigned to each group changed over the years as shown in Table 3.

The use of TV decreased from 50% (1992–1998) to 12.7% (2005–2010) ($P = .0002$), with a nonsignificant increase for NT from 50% to 64.6% ($P = .304$). NRA was not available from 1992 to 1998; it

TABLE 1 Classification of SMA1 Severity According to Age at Onset of Clinical Symptoms⁹

Groups	Number and Proportion (%) of Patients With Symptom Onset <3 Months (True SMA1)	Number and Proportion (%) of Patients With Symptom Onset >3 Months (Intermediate SMA1)
NT (<i>n</i> = 121)	83 (68.5) ^a	38 (31.5)
TV (<i>n</i> = 42)	16 (38.1)	26 (61.9)
NRA (<i>n</i> = 31)	10 (32.2)	21 (67.8)

^a NT versus NRA and TV, $P < .01$.

TABLE 2 Classification of SMA1 Severity According to Age at First Respiratory Decompensation¹⁴

Group	Number and Proportion (%) of Patients With First Respiratory Decompensation Between 0 and 3 Months (Severe SMA1)	Number and Proportion (%) of Patients With First Respiratory Decompensation Between 4 and 18 Months (Typical SMA1)	Number and Proportion (%) of Patients With First Respiratory Decompensation After 18 Months (Mild SMA1)
TV (<i>n</i> = 42)	1 (2.3)	33 (78.5)*	8 (19)
NRA (<i>n</i> = 31)	5 (16.1)	15 (48.3) [§]	11 (35.4)

[§]NRA versus *TV, $P < .05$.

successively increased from 8.1% (1999–2004) to 22.7% (2005–2010) ($P = .021$).

At the time of the study, 113 patients (93.3%) had died at a median age of 6.95 (mean age: 8.1 ± 5.3 months; interquartile range: 5–10.1 months), 7 patients (16.7%) died at a median age of 76.1 months (mean age: 85.6 ± 46.7 months; interquartile range: 51.5–113.1 months), and 14 patients (45.2%) died at a median age of 28.6 months (mean age: 31.6 ± 21.3 months; interquartile range: 12.8–41.4 months) in the NT, TV, and NRA groups, respectively. Survival at 24 and 48 months was higher in TV users than in NRA users: 95% (95% confidence interval [CI]: 81.8%–98.8%) and 67.7% (95% CI: 46.7%–82%) at 24 months ($P < .001$) and 89.43% and 45% at 48 months in the TV and NRA groups, respectively ($P < .001$). Some patients with mild

phenotypes in the NT group survived beyond 24 months (1.3% [95% CI: 0.1%–6%] survival in the NT group) (Fig 1).

Table 4 shows the number of respiratory decompensations treated at home or causing patient hospital admissions. Among NRA patients, 7 were eventually tracheostomized: 2 patients (mean age: 22 ± 0.5 months) after 10.1 ± 0.5 months because parents were unable to guarantee the continuous care needed for NRA; 4 patients (mean age: 10.7 ± 1 months) after 2 ± 0.5 months because of an incapability to manage NRA in the presence of the continuous need for bag and mask ventilation; and 1 patient (aged 67 months) after 59 months of NRA because of worsened neurologic status after cardiorespiratory arrest at home.

Fifty-two patients were still alive (89 ± 43 months for TV and 38.2 ± 21.4 for NRA) at the time of data collection. Hours per day of ventilator dependence at data collection were 23.1 ± 2.8 and 12.4 ± 6.07 for TV and NRA groups, respectively ($P < .001$).

In the TV group, all patients depended on mechanical ventilation for 24 hours per day; in the NRA group, only 2 patients needed mechanical ventilation for 24 hours per day, while none needed mechanical ventilation for 18 hours per day.

DISCUSSION

Our data revealed that (1) patients in the NT group had a lower survival probability and died within the second year of life; (2) both TV and NRA patients had a higher survival probability compared with NT patients, with a lower survival probability at 24 and 48 months and a higher risk of death for the NRA group; (3) the hours per day on mechanical ventilation during the study period were significantly less in the NRA group, with just 2 patients being ventilated in the NRA group >18 hours per day.

We observed more respiratory decompensations and treatment failures in the NRA group, which required TV in 7 patients. Importantly, 1 patient suffered from a cardiorespiratory arrest at the age of 5 years because of an unsuccessful resuscitation followed by severe neurologic damage. As already suggested by Bach et al,¹⁰ acute respiratory decompensation can be life-threatening in SMA1 patients. In NRA patients, there are also more difficulties in clearing airways and in performing resuscitation maneuvers due to bulbar dysfunction. Patients in the TV group showed a trend toward fewer respiratory decompensations and emergency hospital admissions than those in the NRA group. Although TV does not completely protect the airway because tracheotomy tubes are often uncuffed, the likelihood of an efficient ventilation is doubtlessly easier in patients in the TV group. These data may indicate that NRA has several limitations and cannot offer the same probability of survival as TV. These data are in contrast with those published in other studies.^{9–11}

Interestingly, in the NRA group, 6 patients (19.3%) did not show any episode of respiratory decompensation and 11 patients (35.4%) had the first respiratory decompensation only after the age of 18 months. This high individual variability was attributed to 1

TABLE 3 Number of Patients Assigned to Each Group

Group	Period		
	1992–1998	1999–2004	2005–2010
NT	5 (50)	45 (60.8)	71 (64.6)
NRA	0 (0)	6 (8.1)	25 (22.7) ^a
TV	5 (50) ^b	23 (31.1)	14 (12.7)
Total	10	74	110

Data are n (%).

^a 2005–2010 vs 1999–2004, $P < .005$.

^b 1992–1998 vs 2005–2010, $P < .005$.

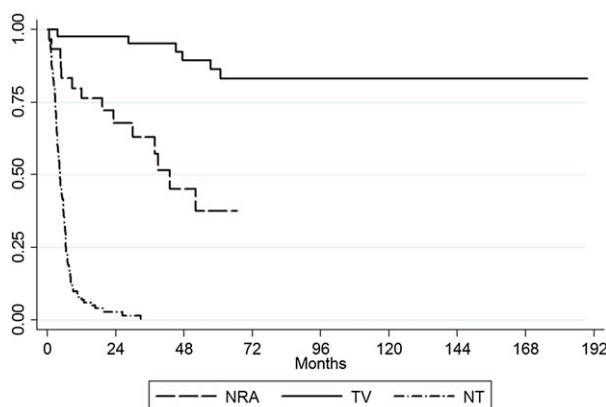


FIGURE 1

Kaplan-Meier estimates of survival in the 3 groups. The cumulative probability of survival was greater for continuous NRA and TV groups, with a lower survival probability at ages 24 and 48 months in the NRA group.

TABLE 4 Number of Respiratory Decompensations During the Entire Study Period

Group	Number of Respiratory Decompensations Treated at Home (Episodes/Patient per Year)	Number of Respiratory Decompensations Needing Hospital Admission (Episodes/Patient per Year)
NRA	42 (0.02)	43 (0.023)
TV	80 (0.007)	71 (0.006)
Total	122	114

patient in need of NIV 24 hours per day since birth and by 1 patient with the first episode of respiratory decompensation at the age of 42 months. Last, at the time of data collection, only 2 out of 31 patients (7%) in the NRA group were in need of NIV 24 hours per day compared with 39 out of 42 patients (92%) in the TV group. These data could indicate that patients treated with NRA could have a milder phenotype as recently suggested.²² Previous studies also found that tracheostomy makes patients more dependent on the ventilator.²⁴

Mortality in our cohort treated with NRA was higher (45.2%) than that reported by others.^{10–12,16} Bach et al¹¹ reported a mortality rate of 17% (8 of 47 treated patients) in NRA patients aged 65.2 ± 45 months. A recent study from a single Italian center also revealed that the mortality rate was 14.2% in 16 NRA users aged 40.5 ± 18.1 months.¹² However, the mortality rate was higher in other studies.^{25–27} Chatwin et al,²⁶ in a study in children treated with NRA, whose age was not reported, observed a mortality rate of 38.4%. Mannaa et al,²⁷ using low levels of bilevel ventilation, found no prolongation of survival with all deaths within the second year of life, which was equal to that of the untreated patient. Because the mortality rates of the current study is

among these results, we can speculate that differences may derive from changes in treatment to NRA and an improved learning curve over the years. Moreover, NIV has gradually become more available over the past 10 to 20 years in Italy, which also affects treatment choice.

Our study has several limitations. First, it was a retrospective case series; however, to our knowledge, no randomized controlled trial has been carried out in SMA1 management up to now.²⁶ Second, we first ranked SMA severity according to loos et al⁸ because we lacked data on the age at first episode of respiratory decompensation of the nonventilated patients. Third, NIV and MAC have been used differently over the years among the referring units, reflecting a possible nonhomogeneous ventilatory treatment.²⁸ Fourth, NT, NRA, and TV groups were likely not homogeneous. It is also possible that some patients affected by severe disease had been assigned to NRA to allow for compassionate discharge from the hospital. Fifth, tracheal ventilation or NRA requires different levels of caregiver expertise. It cannot be excluded that some deaths in the NRA group could be related to caregiver inexperience, inadequate training, or to a delay in hospital admission. Sixth, our results are from referral care hospitals with

experienced multidisciplinary teams. Our results may not be applicable to nonreferral centers.¹² Seventh, clinicians at the different hospitals could have presented the parents with the choices in a different fashion. One cannot exclude that children affected by the most severe phenotypes induced physicians and consequently parents to choose for an NT strategy.²⁵ However, the number of “true” SMA1⁸ patients was higher in the NT group compared with the TV and NRA groups, suggesting a parental choice for NT because of a worse quality of life in these children.

In conclusion, long-term survival outcome can be determined by parents' choice. NRA and TV presented as therapeutic options can prolong survival, with NRA showing a lower survival probability at ages 24 and 48 months. There is no ideal respiratory treatment of patients with SMA1. NRA has several limitations, some of which may be severe, such as the risk of unsuccessful resuscitation at home during respiratory decompensations. In addition, the higher risk of hospitalization, which may include intermittent patient intubation, may impair quality of life for the patient's family and the patient's healthy siblings. These limitations are not due only to caregivers' or clinicians' inexperience but also to the severity of the disease itself and the equipment for NRA, which was originally designed for teenage and young adult patients.²⁹ We believe that our results may help clinicians involved in the care of patients with SMA1 to be more aware of survival trends using different strategies.

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