Stander Use in Spinal Muscular Atrophy: Results From a Large Natural History Database

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Purpose: The purpose of this study was to describe stander use in a natural history cohort of drug therapy-naïve children with spinal muscular atrophy (SMA) who are not walking and identify factors associated with consistent stander use.
Methods: Data from 397 children with SMA types 1 and 2 characterized the prevalence and frequency of stander use. Predictors of consistent stander use explored were SMA type, survival motor neuron 2 gene (*SMN2*) copy number, respiratory support, and motor performance.
Results: Prevalence of consistent stander use was 13% in type 1 and 68% in type 2. SMA type, *SMN2* copy number, respiratory support, and head rotation control each predicted consistent stander use.
Conclusions: Findings characterize stander use in children with SMA who are not walking, address important safety considerations, identify factors that may inform physical therapists' clinical decision-making related to standing program prescription, and provide guidance for future prospective studies. (Pediatr Phys Ther 2020;32:235–241)
Key words: adverse events, Functional Motor Scale Extend, intervention, Modified Hammersmith Functional Motor Scale-Extend, motor performance, respiratory support, spinal muscular atrophy, stander use, supported standing, Test of Infant Motor Performance Screening Items, weight bearing

INTRODUCTION AND PURPOSE

Spinal muscular atrophy (SMA) is a recessive degenerative motor neuron disease caused by deletion or mutations in the *survival motor neuron 1* (*SMN1*) gene.[1] The resulting survival motor neuron (SMN) protein deficiency leads to progressive muscle weakness and atrophy.[2] SMA remains a leading genetic cause of infant death and one of the common neuromuscular disorders, with an incidence of 1 in 10 000 births.[3] Importantly, the *SMN1* gene has a highly homologous gene known as survival motor neuron 2 gene (*SMN2*), which functions as a backup gene and makes SMN protein, although in insufficient amounts to prevent disease. The number of *SMN2* copies is inversely related to and serves as one predictor of disease severity.[2,4]

Clinical phenotype in SMA is heterogeneous, with onset from the prenatal period to adulthood. SMA type 1 (early infantile onset) accounts for more than 50% of all incident cases and is characterized by symptom onset within the first 6 months of life, inability to sit or stand independently at any point in development, and moderate to severe respiratory compromise. Most of these infants have 2 copies of the *SMN2* gene.[5,6] SMA type 2 (late infantile onset), a moderate to severe form with longer life expectancy and the potential for survival well into adulthood, is typically diagnosed later in infancy, prior to 18 months of age. The highest level of motor abilities typically achieved in SMA type 2 is independent sitting and, for some children, standing or stepping with support.[5] Scoliosis is the most common orthopedic impairment in SMA type 2 and can lead to instability and pressure points in seating, reduced lung function, and worsening of contractures.[7,8] Children with SMA type 2 most commonly have 3 copies of the *SMN2* gene, but there is some variation.[2,4] Maximal motor function achieved in infancy or early childhood, regardless of *SMN2* copy number,

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previously defined SMA subtype based on children who cannot sit (type 1), and children who can sit but cannot walk (type 2). However, the availability of novel disease-modifying therapies and the push toward implementation of newborn screening to allow for early, even presymptomatic, treatment interventions are beginning to dramatically change the course of this disease.[9]

Supported standing has been advocated for children who do not walk and have SMA in light of potential benefits for improved bone density,[10,11] spinal alignment, muscle length,[12] gastrointestinal function, pulmonary health, and cognitive and social engagement.[13-16] The 2007 SMA care standards recommended supported standing with bracing for children with SMA type 2 only, and did not provide guidance for frequency of stander use.[16] Recently updated care standards recommend that supported standing be considered for children with both SMA types 1 and 2, with a recommended "optimal" frequency of 5 to 7 times per week.[17,18] Both sets of care standard recommendations related to supported standing were based on expert consensus, given a lack of natural history and experimental studies addressing use of standing programs in children who do not walk and have SMA.

Therefore, we used a large SMA natural history dataset to address 2 aims: (1) to characterize stander use and frequency of use in children with SMA types 1 and 2 and (2) to identify early disease severity and motor function factors associated with supported standing that may be used to guide physical therapists' clinical decision-making related to standing program prescription. Potential predictors of stander use explored in this study included SMA type, *SMN2* copy number, early use of respiratory support, and early motor performance, including head, trunk, and sitting control. SMA type and copy number were included as known indicators of disease severity.[4,6] Early use of respiratory support was selected, given known differences and variability of respiratory care practices during the period in which these data were collected, before widespread adoption of the care standards recommending proactive ventilatory support for all symptomatic children and those unable to sit.[16,17] We anticipated that the nature of the relationship between respiratory support and stander use might be different between children with SMA types 1 and 2, and hypothesized that, in children with type 1, use of early respiratory support as part of proactive care management might improve the odds of a consistent standing program. Infant motor performance was included as a functional indicator of disease severity.[19,20]

METHODS

Study Design and Participants

This was a retrospective cohort study of 397 children with SMA (188 type 1 and 209 type 2) followed up between 2004 and 2015 and enrolled in the Project Cure SMA natural history study. This cohort of children was followed up before effective disease-modifying gene and drug therapies, including the first Food and Drug Administration (FDA)-approved treatment, nusinersen (Spinraza) and more recently approved AVXS-101 (Zolgensma), were available. Age range at study enrollment was 0 to 4.5 years for children with type 1 and 0 to 11 years for children with type 2. Study visits typically occurred every 4 to 6 months. Not all children had available data for all analyses (Figure 1). Data from 36 participants with SMA type 1 who died before a 9-month appropriate developmental age for standing were excluded from analyses. The initial study was approved by the Institutional Review Board (IRB) of the University of Utah and all participating sites, which included 6 US centers and 1 center each in Europe and Canada. Participants had written informed parental consent. Written and/or verbal assent was obtained for children 7 years and older. Deidentified data for analysis were obtained from the Project Cure SMA Longitudinal Pediatric Data Repository, initially approved by the University of Utah IRB and currently maintained under the Partners Healthcare IRB for Massachusetts General Hospital.

Tests and Measures

Medical history information, including SMA type (based on maximum achieved motor function), *SMN2* copy number, and respiratory support status, was collected at regularly scheduled clinic visits. Reliable and valid motor performance measures, including the Test of Infant Motor Performance Screening Items (TIMPSI)[20] or Modified Hammersmith Functional Motor Scale-Extend (MHFMS-Extend),[21,22] were administered by a physical therapist experienced in SMA and trained in SMA outcome measures. The TIMPSI was used for children with SMA type 1 and young children with type 2 who had not yet met the developmental milestone of sitting. The MHFMS-Extend was used for children older than 18 months with SMA type 2 who could follow instructions and sit independently. Caregiver reports of stander use and frequency of use were collected

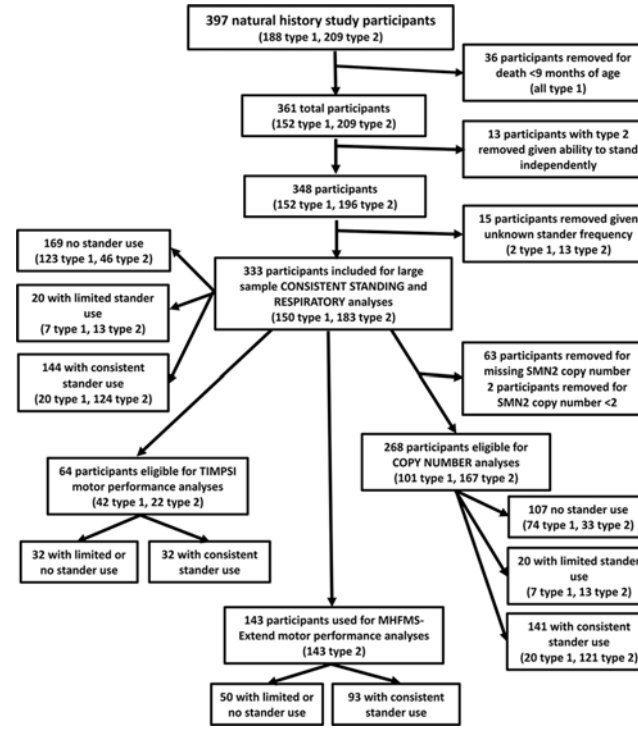

Fig. 1. CONSORT flow diagram.

as part of the physical therapy evaluation at each clinic visit. Supported standing programs included use of a supine stander, mobile stander, or parapodium. Examples of children with SMA engaged in supported standing are in Figure 2. Data were recorded using standardized forms, then entered, checked, stored, and managed in a Research Electronic Data Capture (REDCap) database, the Project Cure SMA Longitudinal Pediatric Data Repository.[23]

TIMPSI items characterizing head control (Item 14: head rotation side to side; item 15: head control in supported sitting; item 41: lateral head righting) and supported standing (item 40) were chosen as a priori stander use predictor variables for participants with TIMPSI data available (n = 64). The TIMPSI data point between 9 and 24 months of age and closest to 12 months was used. Twelve months of age is developmentally relevant for pulling to stand and standing, making the 9- to 12-month window a key time for physical therapy clinic decision-making related to stander use.[14] MHFMS-Extend items characterizing motor control in sitting (item 1: unsupported sitting; item 2: unsupported long sitting) and standing (item 18: stands with one hand; item 19: stands independently) were chosen as a priori stander use predictor variables for participants with MHFMS-Extend data available (n = 143). The MHFMS data point between 18 and 48 months of age and closest to 24 months was used to target an age for reasonable child cooperation and reliable and valid test results.[22] Children without available motor performance data were excluded from MHFMS-Extend/TIMPSI analyses. Children with type 2 SMA who had both TIMPSI and MHFMS-Extend data collected at different visits were included in both motor performance test analyses (n = 13).

Statistical Analysis

Respiratory support data were dichotomized into 2 levels: (1) used respiratory support at any point in time between 6 and 24 months (bilevel positive airway pressure [BiPAP] or mechanical ventilation) and (2) did not use respiratory support between 6 and 24 months of age. Frequency of stander use data was dichotomized into 2 levels: (1) consistent stander use (daily; 3-5x/week) and (2) no/limited stander use (1-2x/week; occasionally; none). The highest frequency of stander use reported across the period of data collection was used. To address aim 1 (characterize stander use in this sample), descriptive statistics were generated for SMA type, *SMN2* copy number, stander use and frequency of use, and respiratory support status. To address aim 2 (identify early disease severity and motor function factors associated with stander use), logistic regression analyses were used to generate odds ratios (ORs) with 95% confidence intervals (CIs). Independent variables in the initial backward selection regression models were SMA type, *SMN2* copy number, respiratory support between 6 and 24 months of age (yes/no), motor performance (TIMPSI or MHFMS-Extend total scores), and motor control (head, sitting, and standing control item scores). Given collinearity among predictors, subsequent logistic regression analyses used individual variables and/or separated SMA types 1 and 2.

RESULTS

After removing the data of those who died before 9 months of age from the full natural history cohort of 397, the remaining natural history study sample of 361 infants and children included 152 (42%) with SMA type 1 and 209 (58%) with type 2 (Figure 1). Thirty percent had 2 *SMN2* copies, 45% had 3 copies, 7% had 4 copies, and in 18% copy number was unknown (Table 1). Thirteen of 361 children (all with SMA type 2) stood independently at some point in time and were excluded from subsequent stander use analyses (Figure 1). The mean number of visits for the remaining cohort of 348 children was 10 (range 1-65 visits) and 302 (87%) were followed up across multiple visits. Of the 46 children seen for a single visit, 14 died, and 32 were lost to follow-up. Children with more than 1 visit were followed up for a mean of 3.3 years (range 1-14 years). Known death occurred in 56 of 348 (16%) of children after 9 months of age, 48 of whom (86%) had SMA type 1. Mean age of death for the 48 with SMA type 1 was 6 years (range 10 months to 41 years). Mean age of death for the 8 children with SMA type 2 was 16 years (range 2-49 years).

Consistent Stander Use

Frequency of stander use data was available for 333 of 348 (96%) eligible children. Frequency counts for stander use by SMA type and copy number are in Table 2.

The prevalence of any stander use in this sample was 164 of 333 (49%). The prevalence of consistent use (≥3 times per

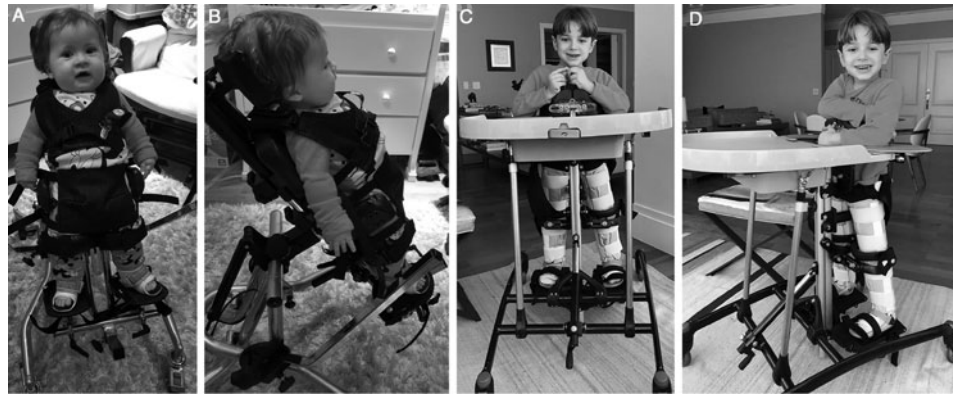

Fig. 2. Stander use in children with spinal muscular atrophy types 1 (A and B, supine stander) and 2 (C and D, parapodium).

TABLE 1

Demographics

	SMA Type 1	SMA Type 2	Total
Total participants	*152 (42%)*	*209 (58%)*	*361*
Male	73 (48%)	115 (55%)	188 (52%)
Female	79 (52%)	94 (45%)	173 (48%)
1 copy *SMN2*	2 (1%)	0	2 (<1%)
2 copies *SMN2*	97 (64%)	11 (5%)	108 (30%)
3 copies *SMN2*	5 (3%)	158 (76%)	163 (45%)
4 copies *SMN2*	1 (1%)	24 (11%)	25 (7%)
Unknown *SMN2* copies	47 (31%)	16 (8%)	63 (18%)
Respiratory support			
No	66 (43%)	141 (68%)	207 (57%)
Yes	86 (57%)	55 (26%)	141 (39%)
Unknown	0	13 (6%)	13 (4%)
Motor Function Scores	**Type 1 Mean (Range)**	**Type 2 Mean (Range)**	**Types 1 and 2 Mean (Range)**
TIMPSI	28 (5-56)	49 (6-89)	35 (5-89)
MHFMS-Extend	NT	13 (0-35)	13 (0-35)

Abbreviations: MHFMS-Extend, Modified Hammersmith Functional Motor Scale-Extend; NT, not tested; SMA, spinal muscular atrophy; *SMN2*, survival motor neuron 2 gene; TIMPSI, Test of Infant Motor Performance Screening Items.

week) was 144 of 333 (43%), 20 of 150 (13%) in the type 1 group and 124 of 183 (68%) in the type 2 group. Of the 164 children with reported stander use, consistent use was reported for 88%, 20 of 27 (74%) with SMA type 1 and 124 of 137 (91%) with type 2. Consistent stander use was reported for 1 child as young as 6 months of age for each SMA type group. *SMN2* copy number analysis (for the subgroup of n = 268 with known copy numbers) showed consistent stander use for 26 of 107 (24%) children with 2 *SMN2* copies, 100 of 141 (71%) with 3 copies, and 15 of 20 (75%) with 4 copies.

Both SMA type (1 vs 2) and *SMN2* copy number (2 vs 3 vs 4) independently predicted consistent stander use for the sample of 268 children for whom copy number was 2 to 4 and known (Figure 3). Children with SMA type 2 were 11 times more likely to engage in consistent stander use than those with type 1 (OR = 10.7, 95% CI, 5.9-19.3; $P < .0001$). Compared with children with 2 copies of *SMN2*, those with 3 copies were 8 times more likely to engage in consistent stander use (OR = 7.6, 95% CI, 4.3-13.5; $P < .0001$) and those with 4 copies were 9 times more likely to engage in consistent stander use (OR = 9.3, 95% CI, 3.1-28.6; $P < .0001$). Children with 3 and 4 *SMN2* copies were equally likely to engage in consistent stander use.

Use of respiratory support between 6 and 24 months of age was reported for 86 of 152 (57%) children with type 1 and 55 of 209 (26%) children with type 2 (Table 1). Based on the sample of 150 children with SMA type 1 for whom all relevant respiratory and stander use data were available, those who used respiratory support were 18 times more likely to engage in consistent stander use than those who did not use respiratory support (OR = 18.4, 95% CI, 2.4-34.4; $P \leq .005$; Figure 3). Nineteen of the 20 (95%) children with SMA type 1 who consistently used a stander also used early respiratory support between 6 and 24 months of age. No significant association was present between respiratory support and consistent stander use in the sample of 183 children with SMA type 2 for whom all relevant respiratory and stander use data were available.

Motor performance total scores for the TIMPSI (closest to 12 months of age) and MHFMS-Extend (closest to 24 months of age) were not associated with stander use. In the sample of 64 infants (42 type 1 and 22 type 2) with available TIMPSI and stander use data, head control at 12 months of age (indexed by item 14: head rotation side to side) was associated with supported standing. Every 1-point increase in head rotation item score (scale 0-5) was associated with a greater than 2-fold increase in the odds of consistent stander use, with respiratory status controlled (OR = 2.4, 95% CI, 1.3-4.2; $P = .005$). No other TIMPSI or MHFMS-Extend items related to head, sitting, or standing control were associated with consistent stander use.

Serious Adverse Events Associated With Stander Use

Of the 164 children with known frequency of stander use over the 11-year study period, 2 serious adverse events (SAEs) were documented with stander use. Both events involved children with SMA type 1 who were older than 5 years, and both occurred while the child was briefly left in the stander unsupervised. In 1 case, there was documented cardiac arrest with subsequent resuscitation by the child's mother, resulting in some permanent neurologic deficit following recovery. In the second case, there was respiratory arrest requiring resuscitation,

TABLE 2

Stander Use Frequency by Type and *SMN2* Copy Number

	Any Stander Use	Consistent Stander Use[a] Consistent (Daily; 3-5x/wk)	Limited Stander Use ≤ 2x/wk	No Stander Use	Total
Total participants	*164*	*144 (124; 20)*	*20*	*169*	*333*
Type 1	27	20 (14; 6)	7	123	150
Type 2	137	124 (110; 14)	13	46	183
SMN2 = 1	0	0	0	2	2
SMN2 = 2	34	26 (19; 7)	8	73	107
SMN2 = 3	111	100 (90; 10)	11	30	141
SMN2 = 4	16	15 (13; 2)	1	4	20
SMN2 = Unknown	3	3 (2; 1)	0	60	63

Abbreviation: *SMN2*, survival motor neuron 2 gene.

[a]Consistent stander use was defined as daily stander use or 3-5x/week stander use.

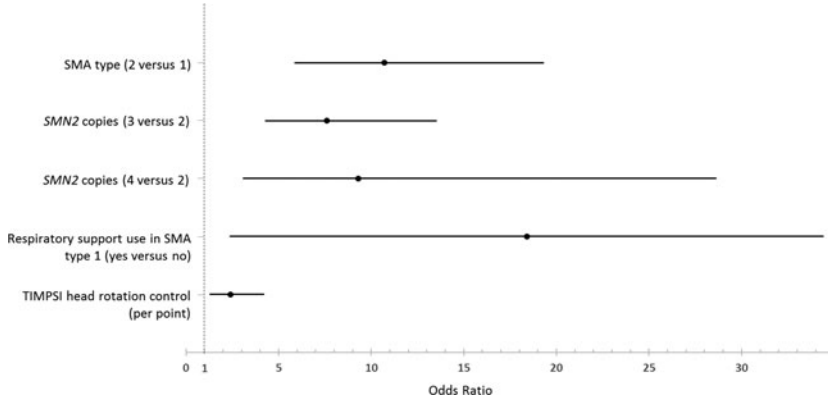

Fig. 3. Forest plot of significant odds ratios for consistent stander use analyses with 95% confidence intervals.

after which the child recovered to baseline without additional intervention.

DISCUSSION

Current SMA standard of care guidelines recommend supported standing as a part of best practice intervention for children with SMA types 1 and 2 based on expert consensus, with an optimal dose of 5 to 7 times/week.[17,18] However, empirical data to help guide prescription of supported standing programs among nonambulatory infants and young children with SMA remain limited. We present the first quantification of stander use in a large natural history cohort of children who do not walk and have SMA types 1 or 2.

Supported standing was reported for nearly half (49%) of the infants and children with SMA in this natural history sample who were not walking. For children engaged in a standing program, consistent stander use was achieved by nearly 9 of 10 (88%). In our "consistent" stander use analyses, we included children for whom reported use was daily or 3 to 5 times/week, as these frequencies have shown potential therapeutic value for other populations of nonambulatory children.[10,13,14,18] Although this was an historical sample of children followed before care guidelines for standing frequency were published, 76% of children in this cohort who used a stander did so daily and met the current 5 to 7 times/week guideline recommendation for "optimal" frequency. These findings provide evidence to support the feasibility of daily standing programs for many children who have SMA and do not walk.

Stander use was significantly more likely in children with SMA type 2 (who achieved the ability to sit at some point during development) than in those with type 1 (who did not achieve independent sitting). Most children with SMA type 2 (68%) engaged in consistent stander use. Notably, 1 of 10 children with SMA type 1 also engaged in consistent stander use, despite the presence of profound weakness requiring multijoint lower extremity bracing and significant trunk and head support to maintain a supported upright position. Consistent stander use is achievable by some children with SMA type 1 who are drug-therapy naive.

We identified additional disease severity factors beyond SMA type, as well as early function factors, associated with consistent stander use. These factors included higher *SMN2* copy number (3 or 4), use of respiratory support (in children with SMA type 1), and head rotation control (in both children able and unable to sit). The odds of consistent stander use in weaker children with type 1 who never achieved sitting was significantly higher in children who used respiratory support, compared with those who did not require or use support before 24 months of age. Respiratory support in this sample included any daytime, nighttime, or intermittent noninvasive respiratory support (BiPAP). Given that 19 of 20 children with SMA type 1 who used a stander consistently also had respiratory support before 2 years of age, improved ventilation may support stander use in some children who are unable to sit. Stander use and use of respiratory support may simply both be elements of a more proactive care approach by the multidisciplinary care team and/or family, and a causal link may not exist. Regardless, the findings support the idea that a supported standing program is feasible for some weaker, fragile children who require invasive or noninvasive ventilatory support.

Although the cohort of children able to sit (type 2) was more likely to use a stander consistently, motor control between 18 and 48 months of age and closest to 24 months in this cohort was not predictive of stander use. The lack of association between sitting motor control and stander use in this study was unexpected. Existing SMA research has identified "hands-free sitting" as one factor to consider in clinical decision-making related to prescription of standing.[24] Of the motor control variables explored in this study, only head rotation control at 12 months of age was associated with consistent supported standing. Independent head control is not a prerequisite to a supported standing program, since a supine stander allows varying degrees of tilt and the head can be stabilized using external support, if needed. However, the ability of a child to turn the head when supported upright provides an opportunity to track, engage, and interact with people and objects in their environment more readily and fully than with a stabilized head and visual tracking alone, or than from a dependent supine position, perhaps enhancing tolerance of the standing position. Additionally, some degree of head control may support the caregiver's and child's comfort with stander use, given valid concerns about the risk of airway occlusion. Importantly, our head rotation control findings were for the subgroup of children

with TIMPSI data, most of whom had SMA type 1 and lacked full head control, perhaps making the head rotation item a better predictor of stander use than it would be for a sample of stronger patients. In children with SMA type 2, who had better head and sitting control than those with type 1, factors other than motor control may predict stander use. Child motivation, family time commitments, and access to equipment should be further explored in future studies of stander use in children with SMA who are able to sit.

Although SAEs in children with SMA using standing devices appear uncommon (we had 2 SAEs over 11 years in the cohort of 164 children using standers), in those with poor head control and/or profound weakness, external head support and close monitoring of the airway, respiratory and circulatory status during supported standing is critical. We emphasize the need for caregiver education related to safety and direct supervision at all times with stander use in children with SMA, similar to recommendations of the American Academy of Pediatrics for drowning prevention in the bathroom and around water.[25]

Limitations

This study was limited by the retrospective design and lack of detailed data collection about standing prescriptions, including stander type, child's position in the stander, and standing session duration. Stander use was based on caregiver report, which may have introduced the possibility of over- or underestimation of standing frequencies. Respiratory support data were not collected in sufficient detail to stratify by type of support (BiPAP vs mechanical ventilation). Muscle contractures, particularly of the hip flexors, knee flexors, and ankle plantar flexors are prevalent in children who have SMA and do not walk[12] and may limit stander use in children with neuromuscular diseases[14,15]; however, robust muscle length data were not available for use in this retrospective analysis. Finally, smaller sample sizes of the TIMPSI ($n = 64$) and MHFMS-Extend ($n = 143$) analyses relative to respiratory support analyses leave open the possibility that limited statistical power underlies null results for motor performance measures as predictors of stander use.

Future Directions

Supported standing can offer an alternative to, or a functional bridge between, sitting and walking that encourages the development of bone structure and motor control, both critical for mobility. By reporting prevalence of stander use in a large sample of children who do not walk and have SMA, and providing initial evidence pointing to several factors that may be associated with stander use in this population, this work sets the stage for future prospective studies addressing safety, adherence, and efficacy with supported standing interventions. Future studies should explore potential barriers to participation in all children who do not walk and have SMA, including general health of the child, lower extremity contractures, family health literacy, socioeconomic status, social supports, and stresses, as well as medical management, care team use of SMA guidelines, and insurance/equipment funding. Further exploration of stander type, optimal positioning, load, and duration, as well as potential therapeutic benefits of supported standing, including improved bone mineral density, muscle length, respiratory and gastrointestinal health, and functional motor outcomes are needed.

With the availability of new, effective SMA drug therapies (eg, FDA-approved Spinraza and Zolgensma), we are likely to see significantly improved developmental motor potential, including independent standing and walking, in children previously unable to achieve these milestones, particularly when treatment is initiated before or at the earliest signs of symptoms.[26-29] Prioritizing age-appropriate early weight-bearing may be critical in helping drug-treated infants with SMA achieve optimal motor outcomes.

The results from this study indicate that stander use is feasible for many children who have SMA and do not walk. For most children engaged in stander use, a daily standing program was achievable. Factors impacting safety, feasibility, and adherence need further exploration, but likely include sufficient head control to protect airway, adequate supervision, family time and care preferences, the presence of lower extremity joint contractures, and equipment resources.

CONCLUSIONS

Stander use can and should be considered as an intervention for nonambulatory infants with SMA to provide an early, upright weight-bearing experience that models supported standing activities of 9- to 15-month-olds developing typically.[24,30] Physical therapists must ensure that children with limited head control can attain and maintain a supported standing position that protects the airway, and are provided with close supervision during standing. Additional positioning considerations include accommodation for lower extremity contractures, provision of lower extremity bracing support (eg, knee-ankle-foot orthoses or ankle-foot orthoses) to optimize joint alignment and prevent excessive valgus forces at the knee, and placement in slight hip abduction to optimize hip congruence.[14,18] Consistent use of 3 to 7 times per week is usually feasible if stander use is tolerated. Further exploration of optimal dosing parameters, as well as child, family, and environmental variables, is needed to help guide physical therapists' clinical decision-making related to supported standing program prescription in children who have SMA and do not walk.

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