

Evaluation of therapeutic electrical stimulation to improve muscle strength and function in children with types II/III spinal muscular atrophy

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The study aimed to evaluate the effect of low-intensity night-time therapeutic electrical stimulation (TES) on arm strength and function in children with intermediate type spinal muscular atrophy (SMA). The design was a randomized controlled trial with a 6-month baseline control period. Children were evaluated at baseline, 6, and 12 months. TES was applied from 6 to 12 months to the deltoid and biceps muscle, of a randomly selected arm with the opposite arm receiving a placebo stimulator. Thirteen individuals with SMA between 5 to 19 years of age were recruited into the study and eight completed the 12-month assessment. No statistically significant differences between the treatment and control arm were found at baseline, 6, and 12 months for elbow flexors, or shoulder abductors on quantitative myometry or manual muscle testing. There was no significant change in excitable muscle mass assessed by M-wave amplitudes, nor function on the Pediatric Evaluation of Disability Inventory (self-care domain). Therefore, in this study there was no evidence that TES improved strength in children with SMA.

Spinal muscular atrophy (SMA) is a neuromuscular disorder in which atrophy of the anterior horn cells leads to denervation, muscle weakness, and progressive loss of motor function. Genetic linkage for all three types of SMA has been found on chromosome 5q11.2-13.3 (Brzustowicz et al. 1990, Wong and Chan 2001). The excessive early death of motorneurons in SMA is linked to abnormal neuronal trophic factors, abnormal motorneuron-muscle interaction, and to abnormal regulation of programmed cell death (Henderson and Fardeau 1988, Sarnat et al. 1989). When a muscle becomes partially denervated, two types of compensatory processes occur. First, muscle fibers that retain their nerve supply may hypertrophy. Second, there is collateral reinnervation with nerve branching to non-innervated muscle fibers (Wessel 1989).

The milder, more chronic forms, types II (chronic infantile and juvenile) and III (Kugelberg-Welander), are compatible with prolonged survival. In adolescents and adults with SMA, function can deteriorate, however, the number of functioning motor units usually does not decrease further (McComas et al. 1993). It is difficult to determine whether the loss of function is due to progression of the disease, to growth of the child, or to secondary factors such as immobilization (Henderson and Fardeau 1988, Sarnat et al. 1989, Wessel 1989, Russman et al. 1992). In attempting to counteract these secondary changes, researchers have had some success with functional electrical stimulation and high resistance weight training of adults with SMA (McCartney et al. 1988; Milner-Brown and Miller 1988 a,b). Gains in strength were attributed to neural adaptation rather than muscle hypertrophy. Animal studies have also shown positive effects from electrical stimulation of denervated muscle (Herbison et al. 1986, McDevitt et al. 1987).

A form of electrical stimulation that is well tolerated and has been used in children with neuromotor disorders such as cerebral palsy and spina bifida is therapeutic electrical stimulation (TES; Pape et al. 1993, Balcom et al. 1997). It is a low-intensity, night-time, home-based, long-duration electrical stimulation program. The principal objective of this research was to evaluate the effectiveness of TES to improve muscle strength and function in children with chronic SMA after a 6-month period of stimulation to the deltoid and biceps muscles.

Method

PROCEDURE

The study design was a randomized controlled trial with a treatment period of 6 months, preceded by a 6-month baseline control period. TES was used at night-time from 6 to 12 months on the deltoid (shoulder abductor) and biceps (elbow flexor) of a randomly selected arm. The opposite arm received a placebo stimulator (One to One, Stimtrac, Boston, MA, USA) that turned off after 15 minutes of stimulation. The two proximal arm muscles were chosen to standardize the TES application, allow for accurate muscle strength assessment and have muscles that had a range of muscle strength. TES was applied transcutaneously through conductive silicone rubber electrodes. The stimulator was turned on when the participant went to bed and turned off in the morning. The NT-2000 (BMR Neurotech Inc., Phoenix, AZ, USA) is a dual channel battery-operated electrical stimulator generating alternating coupled current pulses. The stimulation

parameters were preprogrammed for this protocol and consisted of a pulse width of 300 μ s, pulse frequency between 35 and 45 Hz, peak intensity less than 10 mA, and a 1:1 on-off cycle. An internal meter measured compliance by recording the number of hours the stimulator had been used. In contrast to functional electrical stimulation (FES), the stimulation current of TES reaches a sensory threshold but does not cause a muscle contraction.

PARTICIPANTS

Individuals with an intermediate form of SMA were recruited from a pediatric neuromuscular clinic at a tertiary level children's treatment center (Bloorview MacMillan Children's Centre, Toronto). Eligibility criteria included the following: clinical diagnoses of SMA, evidence of denervation on electromyography, normal nerve conduction velocities, and age greater than 5 years. A research ethics committee approved this study and written informed consent was obtained.

OUTCOME MEASURES

Outcome measures were obtained in a blinded manner at baseline, 6, and 12 months. Measures included quantitative myometry, manual muscle testing, maximum evoked muscle response amplitudes (M waves), and the Pediatric Evaluation of Disability Inventory (Haley et al. 1992).

Quantitative myometry testing (QMT)

Maximum voluntary isometric contraction was chosen as the primary outcome measure to assess muscle strength. The quantitative myometry testing system (Biomechanical Designs Ltd., Edmonton, Alberta, Canada) was used (Personius et al. 1994). The system consists of an adjustable cuff connecting the participant's arm to a non-compliant strap attached to a force transducer. This transducer can load between 0.5 and 1000 Newtons (N). It allows the measurement of muscle strength on a continuous linear scale and has been shown to be accurate over a wide range of muscle strength. Measurements were obtained bilaterally for shoulder abduction and elbow flexion. The participant was instructed to pull against the strap for a 5-second maximal contraction. This occurred three times with a 10-second rest in between tries. The maximum value was recorded.

Table I: Participant characteristics

Characteristic	Mean (SD)
Age (y)	9.9 (3.36)
Sex M/F	10/3
SMA Type II/III	7/6
Baseline MRC grade – elbow flexors	6.33(2.1)/6.33(2.2)
Treatment/control	
Baseline MRC Grade – shoulder abductors	4.9(2.8)/4.9(2.6)
Treatment/control	
Baseline QMT – elbow flexors	19.08(15.1)/14.81(13.06)
Treatment/control	
Baseline QMT – shoulder abductors	8.97(7.5)/8.49(6.22)
Treatment/control	

SMA, spinal muscular atrophy; MRC, Medical Research Council Scale; QMT, quantitative myometry testing.

Manual muscle testing (MMT)

Manual muscle grading with the modified Medical Research Council scale was used as a secondary outcome measure to evaluate strength. This scale has a 0 to 10 point system and has good test-retest reliability in children with neuromuscular disorders (Mendell and Florence 1990, Florence et al. 1992).

M-wave amplitudes

An electrophysiological evaluation of the biceps muscle was carried out before and after TES treatment at 6 and 12 months, using maximal M-wave amplitudes as an index of excitable muscle fiber mass. Surface recording electrodes were placed transversely over the biceps muscle with the active electrode close to the main end-plate zone of the muscle and the reference electrode was placed 2cm distally (Galea et al. 1991, 2001).

Pediatric Evaluation of Disability Inventory (PEDI)

The self-care domain of the PEDI was used to assess the potential impact of change in muscle strength on self-care activities. It has been used extensively in children with physical disabilities, and has established reliability, construct validity, and responsiveness to change (Feldman et al. 1990, Coster et al. 1994).

Statistical analyses

A Student *t*-test was done comparing the treated arm to the control arm at 0, 6, and 12 months. The no-treatment period was represented by 0 and 6 month data, and the treatment period by 12-month data. The alpha level was set at 0.017 to account for multiple testing. Correlations, using Spearman's rho, were performed to assess the associations between the change in the findings of QM testing during the treatment period to the initial muscle strength and compliance with TES.

Results

Thirteen individuals were enrolled in the study and nine completed all three evaluations (0, 6, and 12 months). The reason given for the drop out of four individuals was that there were long travel times to the centre. Participant characteristics are described in Table I. SMA classification into type II and type III follows the 1991 International SMA Collaboration (Munsat 1991). Results of the QMT for elbow flexors and shoulder abductors including *p* values are outlined in Figure 1, and MMT in Figure 2. No statistically significant differences between the treatment arm and the control arm were found at baseline, 6, nor 12 months for the QMT or the MMT.

The percentage change in the biceps muscle M-wave amplitudes of treatment minus control arm values between 6 to 12 months was 22.6 (SD 21.1; *p*=0.12). The direction of change in the excitable muscle mass favored the treatment arm but was not statistically significant. The PEDI scaled score at baseline was 72.96 (SD 21.88), at 6 months 75.14 (SD 21.82), and at 12 months 76.66 (SD 20.62). Mean change during the treatment period (6 to 12 months) of 1.53 (SD 2.38) was not significant with *p*=0.11.

Mean number of hours of stimulation was 631 (SD 318). This corresponds to an average use of 4 hours per night. Maintaining electrode placement over the deltoid was difficult,

thereby impacting on compliance. A correlation between compliance and change in the QMT during the treatment period was not found (elbow flexors $r=-0.03$, $p=0.96$, shoulder abductors $r=0.45$, $p=0.26$). An association was also not found between initial muscle strength and change in strength during the treatment period (elbow flexors $r=0.26$, $p=0.07$, shoulder abductors $r=-0.45$, $p=0.22$).

Discussion

In this study of children with chronic SMA, TES was not effective in improving muscle strength or self-care function. The potential mechanism of action for TES in SMA was the enhanced ability of existing motor units to maintain muscle bulk and strength, with the electrical current postulated to have a trophic effect on the muscle fibers and/or intramuscular

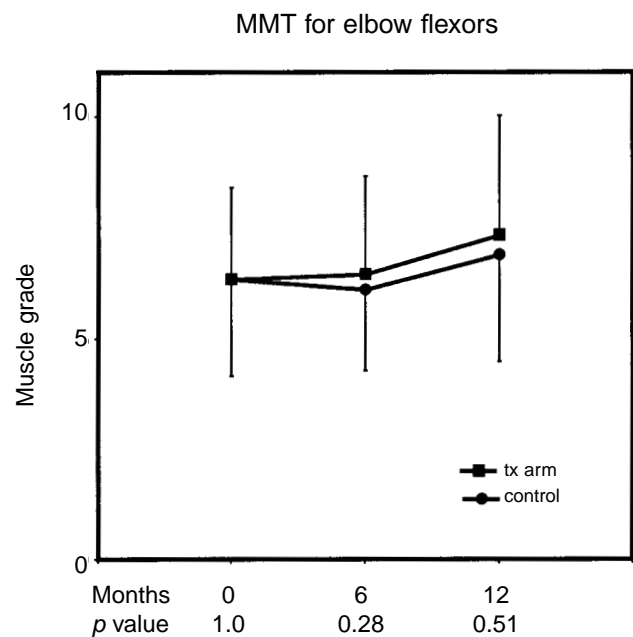
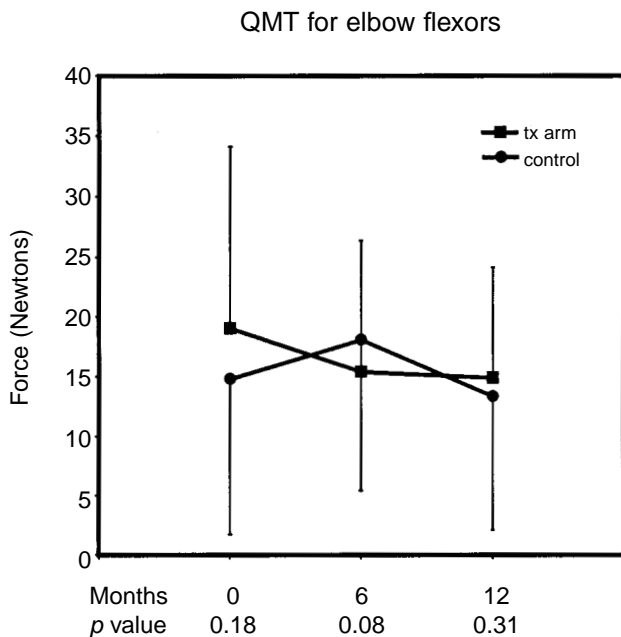
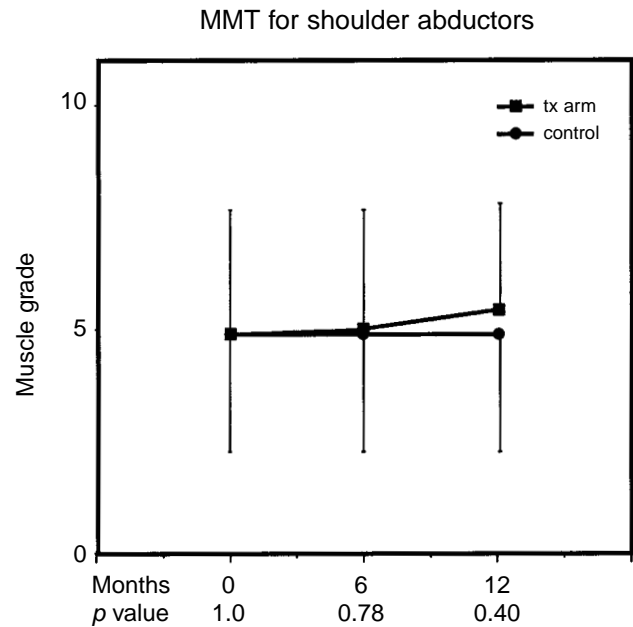
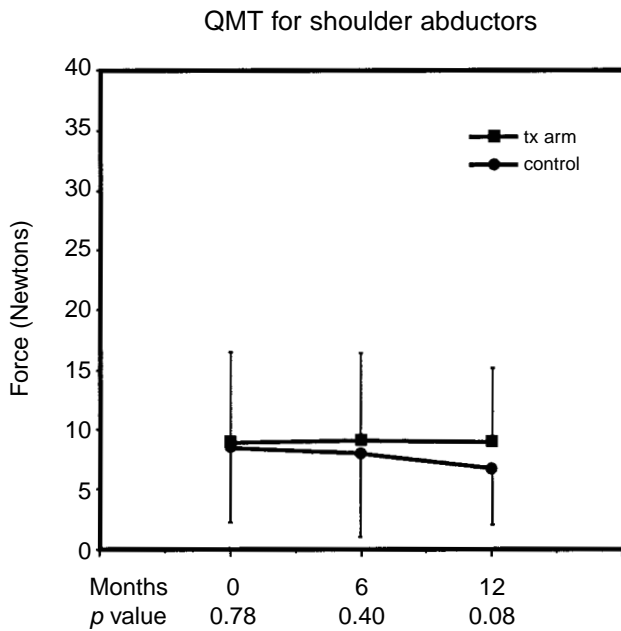


Figure 1: Results of TES on muscle strength of shoulder abductors and elbow flexors over time, measured by quantitative myometry testing (QMT).

Figure 2: Results of TES on muscle strength of shoulder abductors and elbow flexors over time, measured by manual muscle testing (MMT).

nerve branches. The failure of TES treatment suggests an error in the original hypothesis. Providing electrical stimulation to minimize secondary changes in SMA by enhanced activation of surviving 'overworked' motor units may not have enough impact to counteract the primary abnormality of the premature death of a high percentage of motoneurons. Another potential problem with TES is the low level of electrical stimulation applied, which may not effect a change in the motoneuron nor muscle. Perhaps a longer application of TES each night was required. A minimum of 5 hours per night of stimulation is recommended and the average use in the study was 4 hours. However, the authors encourage caution in interpreting this as the sole reason for treatment failure as there was no correlation between compliance and change in muscle strength.

Although this study has a small sample size, given the strength of the study design and the blinded outcome assessments, there is little evidence to support the clinical use of TES in children with SMA. TES's role in treating other childhood neurodisabilities continues to be questioned, with mixed results (Steinbok et al. 1997, Sommerfelt et al. 2001). Further evidence of clinical efficacy is required.

An interesting secondary finding of the study is the assessment of the natural history changes of muscle strength in SMA over a period of 12 months. Strength in the control arm, measured by quantitative myometry and manual muscle testing, remained stable over the 12-month study period. This replicates findings by Iannaccone et al. (2000). The natural history changes plus information on standard deviations for the QMT and MMT will be useful in future SMA research studies.

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References

- Balcom AH, Wiatrak M, Biefeld T, Rauen K, Langenstroer P (1997) Initial experience with home therapeutic electrical stimulation for continence in the myelomeningocele population. *Journal of Neurology* **158**: 1272–6.
- Brzustowicz LM, Lehner T, Castilla LH, Penchaszadeh GK, Wilhelmsen KC, Daniels R, Davies KE, Leppert M, Ziter F, Wood D, Dubowitz V, Zerred K, Hausmanova-Petrusewicz I, Ott J, Munsat TL, Gilliam TC. (1990) Genetic mapping of chronic childhood-onset spinal muscular atrophy to chromosome 5q 11.2-13.3. *Nature* **344**: 540–1.
- Coster WJ, Haley S, Baryza MJ. (1994) Functional performance of young children after traumatic brain injury: a 6-month follow-up study. *American Journal of Occupational Therapy* **48**: 211–18.
- Feldman AB, Haley SM, Coryell J. (1990) Concurrent and construct validity of the Pediatric Evaluation of Disability Inventory. *Physical Therapy* **70**: 602–10.
- Florence J, Pandya S, King WM, Robison JD, Baty J, Miller JP, Sehlerbecker J, Signore LC. (1992) Intrarater reliability of Manual Muscle Test (Medical Research Council Scale) grades in DMD. *Physical Therapy* **72**: 115–26.
- Galea V, De Bruin H, Cavasin R, McComas AJ. (1991) The numbers and relative sizes of motor units estimated by computer. *Muscle & Nerve* **14**: 1123–30.
- Galea V, Fehlings D, Kirsch S, McComas A. (2001) Depletion and sizes of motor units in spinal muscular atrophy. *Muscle & Nerve* **24**: 1168–72.
- Haley SM, Coster SJ, Ludlow LH, Haltiwanger JT, Andrellos PJ. (1992) *Pediatric Evaluation of Disability Inventory (PEDI): development standardization, and administration manual*. Boston: New England Medical Center and PEDI Research Group.
- Henderson CE, Fardeau M. (1988) Nerve growth factors: hypothesis on their role in the pathogenesis of infantile spinal amyotrophies. *Revue Neurologique* **144**: 730–6.
- Herbison GJ, Jaweed M, Ditunno JF. (1986) Electrical stimulation of sciatic nerve of rats after partial denervation of soleus muscle. *Archives of Physical Medicine and Rehabilitation* **67**: 79–83.
- Iannaccone ST, Russmann BS, Browne RH, Buncher CR, White M, Samaha FJ. (2000) Prospective analysis of strength in spinal muscular atrophy. DCN/spinal muscular atrophy group. *Journal of Child Neurology* **15**: 97–101.
- McCartney N, Moroz D, Garner SH, McComas AJ. (1988) The effects of strength training in patients with selected neuromuscular disorders. *Medicine and Science in Sports and Exercise* **20**: 362–8.
- McComas AJ, Galea V, de Bruin H. (1993) Motor unit populations in healthy and diseased muscles. *Physical Therapy* **73**: 868–77.
- McDevitt L, Fortner P, Pomeranz B. (1987) Application of weak electric field to the hindpaw enhances sciatic motor nerve regeneration in the adult rat. *Brain Research* **416**: 308–14.
- Mendell JR, Florence J. (1990) Manual muscle testing. *Muscle & Nerve* (Suppl.) **S16**–20.
- Milner-Brown HS, Miller RG. (1988a) Muscle strengthening through high-resistance weight training in patients with neuromuscular disorders. *Archives of Physical Medicine and Rehabilitation* **69**: 14–19.
- Milner-Brown HS, Miller RG. (1988b) Muscle strengthening through electric stimulation combined with low-resistance weights in patients with neuromuscular disorders. *Archives of Physical Medicine and Rehabilitation* **69**: 20–4.
- Munsat TL. (1991) Workshop report, International SMA Collaboration. *Neuromuscular Disorders* **1**: 81. (Abstract).
- Pape KE, Kirsch SE, Galil A, Boulton JE, White MA, Chipman M. (1993) Neuromuscular approach to the motor deficits of cerebral palsy: a pilot study. *Journal of Pediatric Orthopedics* **13**: 628–33.
- Personius KE, Pandya S, King WM, Tawil R, McDermott MP. (1994) Facioscapulohumeral dystrophy natural history study: standardization of testing procedures and reliability of measurements. *Physical Therapy* **74**: 253–63.
- Russman BS, Iannaccone ST, Buncher CR, Samaha FJ, White M, Perkins B, Zimmerman L, Smith C, Burhans K, Barker L. (1992) Spinal muscular atrophy: new thoughts on the pathogenesis and classification schema. *Journal of Child Neurology* **7**: 347–53.
- Sarnat HB, Jacob P, Jimenez C. (1989) Spinal muscular atrophy: disappearance of RNA fluorescence of degenerating motor neurons. An acridine orange study. *Revue Neurologique* **145**: 305–11.
- Sommerfelt K, Markestad T, Berg K, Saetesdal I. (2001) Therapeutic electrical stimulation in cerebral palsy: a randomized, controlled, crossover trial. *Developmental Medicine & Child Neurology* **43**: 609–13.
- Steinbok P, Reiner A, Kestle J. (1997) Therapeutic electrical stimulation following selective posterior rhizotomy in children with spastic diplegic cerebral palsy: a randomized clinical trial. *Developmental Medicine & Child Neurology* **39**: 515–20.
- Wessel HB. (1989) Spinal Muscular Atrophy. *Pediatric Annals* **18**: 421–7.
- Wong V, Chan V. (2001) Molecular genetic study of a childhood form of spinal muscular atrophy. *Journal of Child Neurology* **16**: 291–4.