The Effect of Combined Use of Botulinum Toxin Type A and Functional Electric Stimulation in the Treatment of Spastic Drop Foot After Stroke: A Preliminary Investigation

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ABSTRACT. Johnson CA, Burridge JH, Strike PW, Wood DE, Swain ID. The effect of combined use of botulinum toxin type A and functional electric stimulation in the treatment of spastic drop foot after stroke: a preliminary investigation. Arch Phys Med Rehabil 2004;85:902-9.

Objective: To investigate the effect of combined botulinum toxin type A (BTX) and functional electric stimulation (FES) treatment on spastic drop foot in stroke.

Design: Nonblinded randomized controlled trial.

Setting: Hospitals.

Participants: Consecutive sample of 21 ambulant adults within 1 year after stroke with a spastic drop foot, of whom 18 completed the study.

Interventions: The treatment group received BTX injections (Dysport) on 1 occasion into the medial and lateral heads of the gastrocnemius (200U each) and tibialis posterior (400U each) muscles and FES, used on a daily basis for 16 weeks to assist walking. Both groups continued with physiotherapy at the same rate.

Main Outcome Measures: Walking speed, Physiological Cost Index, Modified Ashworth Scale, Rivermead Motor Assessment, and Medical Outcomes Study 36-Item Short-Form Health Survey.

Results: Walking speed increased over 12 weeks in both control ($P=.020$) and treatment groups (nonstimulated, $P=.004$; stimulated, $P=.042$). The baseline corrected (analysis of covariance) increase in mean walking speed at 12 weeks, relative to controls, was .04m/s (95% confidence interval [CI], .003–.090) without stimulation, and .09m/s (95% CI, .031–.150) with stimulation.

Conclusions: Combined treatment effectively improved walking and function. A larger study is needed to quantify the treatment effect and to investigate its impact on quality of life.

Key Words: Botulinum toxin type A; Electric stimulation; Muscle spasticity; Rehabilitation; Stroke.

THERE ARE APPROXIMATELY 100,000 stroke patients admitted to hospital in the United Kingdom annually; 20% die, 20% make a full recovery, and 60% make a partial recovery but have a restricted lifestyle.[1] A conservative estimate is that 20% of survivors have a spastic drop foot.[2] These patients experience difficulty when walking because they are unable to effectively dorsiflex their ankle during the swing phase of walking. The problem arises partly through an inability to activate the ankle dorsiflexors and partly through restraint from the calf muscles.[3] In many, the restraint is due to spasticity; in others, the secondary mechanical resistance offered by the calf is a contributory factor.[4-7] After investigating these patterns of muscle activation during walking, Knutsson and Richards[8] described premature calf activity in one third of the patients with spastic hemiparesis, in which electromyographic activity in the triceps surae began and peaked earlier in the gait cycle when compared with normal gait. In a more recent study, Lamontagne et al[9] identified a relation between the lengthening of triceps surae during the stance phase of walking and electromyographic activity that is indicative of hyperactive stretch reflexes in the hemiparetic limb. Calf spasticity during walking was inversely related to walking speed.

Single-channel functional electric stimulation (FES) applied to the common peroneal nerve, using electrodes attached to the skin to elicit ankle dorsiflexion with eversion, may be timed to the swing phase of walking by using a footswitch. It is effective at increasing walking speed, reducing the effort of walking, and improving heel strike and mediolateral foot stability.[2,10-14] Investigations into the perception of patients using FES showed that confidence in their mobility increased and that walking required less effort.[13] There is evidence that FES has a therapeutic training effect on walking in chronic conditions.[11,15] In addition, it is believed to have an inhibitory effect on antagonist activity—thus reducing calf spasticity when the common peroneal nerve is stimulated[11,16,17]—but clinical evidence remains inconclusive. The effect of FES on mobility in acute stroke has not been established; arguably, early intervention may have better long-term therapeutic benefits.

Botulinum toxin type A (BTX) is a neuromuscular blocker that allows focal treatment of overactive muscles; it is given by intramuscular injection. It is used clinically to improve the balance of activity about a joint, to improve motor control, or to increase tolerance of splinting and passive stretching.[18] BTX is effective in decreasing calf spasticity in stroke patients 4 weeks after injection.[19,20] Burbaud et al[20] found spasticity reduction to be most effective in patients within 1 year of stroke, although Hesse et al[19] found that there were improvements in patients in their second year after stroke. Hesse[19] showed its effectiveness in reducing premature calf activation in soleus during walking. Increases in walking speed were also shown by

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Table 1: Outcome Measures Used at Each Assessment During the Study Period

	Baseline Phase			Intervention Phase			
Outcome Measures	Week 4	Week 2	Week 0	Week 2	Week 4	Week 8	Week 12
Walking speed	X	x	x	x	X	x	x
PCI	X	x	x	x	X	x	x
MAS	X	x	x	x	X	x	x
RMA	X	x	x		X	x	x
SF-36	X				X		x

NOTE. "x" is the assessment performed at this stage.
Abbreviations: MAS, Modified Ashworth Scale; PCI, Physiological Cost Index; RMA, Rivermead Motor Assessment; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey.

Hesse,[19] although Burbaud[20] reported only slight increases in speed that were not statistically significant. A few participants experienced no change in walking speed, with subjective reports of a lack of stability after BTX injection; this was attributed to a reduction in the functionally relevant action of the plantarflexors in midstance.[19]

BTX has, therefore, been shown to reduce spasticity, but evidence for improved walking is unconvincing. Similarly, FES can improve walking, but the evidence that it reduces spasticity is less strong. The rationale for using both modalities was, therefore, to reduce the neurogenic component of calf spasticity using BTX, with FES as an adjunctive therapy[21] to improve gait. The addition of FES may further reinforce calf inhibition and provide a mechanical stretching effect while strengthening the stimulated muscles[22-24] and providing a greater orthotic benefit during walking.

Spastic drop foot frequently causes stroke patients to adopt an abnormal gait pattern that leads to increased extensor spasticity. Once established, such abnormal patterns are difficult to correct.[2,20] By applying these treatments in combination in the early recovery phase, the long-term mobility of stroke patients may be improved.

The objective of this study was to evaluate physiotherapy (PT) alone versus PT with BTX and FES in a subacute (<12mo) stroke population.

METHODS

Study Design and Randomization Process

The study design was a randomized controlled trial (RCT) of 16 weeks, including a 4-week baseline phase. There were 3 baseline assessments and 4 assessments during the intervention phase. All potential subjects, referred by their physicians in the 4 participating centers, were screened for inclusion in the trial. Only subjects who met the selection criteria at the end of the baseline phase (week 0) continued in the study (table 1). All assessments during the study period, including screening of patients, were made by a single research physiotherapist. Participants were assessed at the PT department of their local National Health Service (NHS) hospital. Neither the participants nor the research physiotherapist were blinded to the use of FES, because it was impractical to do so given the obvious muscle contraction, sensation, and stimulated movement produced. Participants were randomized at week 2 when they selected a sealed, unmarked, opaque envelope containing a letter that informed them of their group allocation.

Patient Selection

Participants were recruited from the stroke services of 4 NHS Trusts in southern England according to the following selection criteria: (1) first stroke of cerebrovascular origin with hemiplegia during the previous 12 months; (2) inability to achieve heel strike because of spastic equinus, correctable by FES; (3) a score between 3 and 6 inclusive on the Hauser Ambulation Index[25] (HAI); (4) Modified Ashworth Scale (MAS) score of between 2 and 4; (5) an increased calf stretch response on clinical examination; (6) premature calf activation during gait, identified by surface electromyography; and (7) consent given. Patients were excluded who had (1) any additional medical or psychologic condition that would affect their ability to comply with study protocol; (2) changes in prescribed antispastic medication; (3) prescribed medication that might have influenced heart rate measurements; (4) previous treatment with BTX or FES; and (5) fixed ankle or foot contracture.

Screening Using Surface Electromyography During Gait

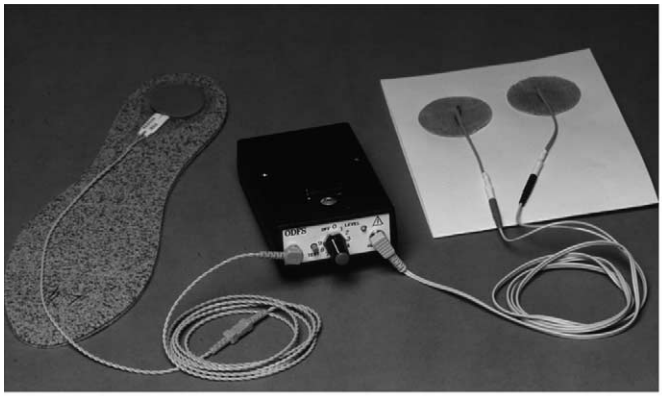
Patients with calf spasticity were screened by clinical examination and by electromyography while walking at their preferred speed over a level linoleum walkway. A portable electromyography system, built in-house, made possible continuous monitoring and averaging of multiple strides. Data were recorded using LabVIEW software[a] on a personal computer. Electromyographic activity of tibialis anterior and the lateral head of gastrocnemius muscles of the affected leg were recorded. Footswitches under the heel and the first metatarsal head were used to define gait events such as heel strike and toe-off. None of the patients reported any hindrance to their walking when the system was worn. From the recorded data of 3 samples of walking, premature calf activity during gait could be identified.[26]

Intervention

All participants received their normal PT program throughout the study period. At the end of the baseline phase, the treatment group received BTX on 1 occasion and began using the drop-foot stimulator (FES). They continued to use the stimulator throughout the trial period (12wk). The control group continued with PT alone. The experimental protocol was approved by the appropriate hospital and local research ethics committees.

Experimental Protocol

Physiotherapy. Participants were treated or supervised by physiotherapists experienced in the treatment of neurologic conditions, independent of the research physiotherapist. PT was given at a similar rate for both groups: twice a week for outpatients and a minimum of 3 times a week for inpatients. Each session lasted approximately 45 minutes. PT was directed toward patient goals and focused on their particular impairments and disability; thus, the specific therapy each patient received varied. Each session was documented, and the type of activity and its duration were recorded.



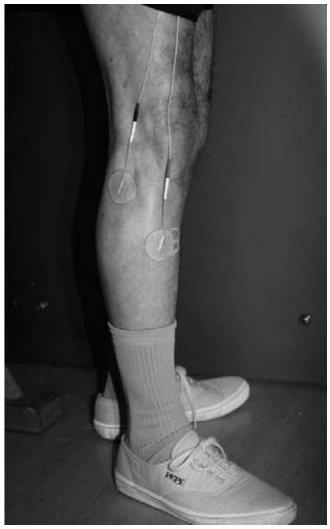


Fig 1. The ODFS III.

BTX injections. Intramuscular injections of BTX (Dysport) were given once to the treatment group participants, immediately after the week 0 assessment. The medial and lateral heads of the gastrocnemius muscle were each injected with 200U of Dysport, and 400U of Dysport were injected in the tibialis posterior, diluted in 4mL of normal saline. The maximum dose of 800U of Dysport was modified for less spastic muscles or smaller patients. Injections were given under electromyographic guidance with MyoJect 26-guage needles[b] that were 37mm in length and coated with polytetrafluoroethylene. Two sites were used close to the motor point of the muscle. If patients were receiving anticoagulant therapy, only 1 site per muscle was used, with 1 minute of manual pressure applied after the injection, to minimize the risk of hemorrhage. Injections were given by 1 physician.

Functional electric stimulation. FES was used after the week 0 assessment to help the treatment group with their mobility. The Odstock Dropped Foot Stimulator mark III[c] (ODFS III) is a portable, single-channel, neuromuscular stimulator (fig 1) used to elicit ankle dorsiflexion and eversion during the swing phase of walking. Usually, the common peroneal nerve is stimulated and timed to a person's walking speed by a footswitch placed in the shoe. The device delivers a train of biphasic electric impulses via surface electrodes at a frequency of 40Hz, with user-controlled pulse width between 30 and 350μs and current amplitude of up to 100mA set by the clinician. The ODFS III was adjusted and set up by the research physiotherapist following the standard procedure.[11] Treatment group participants were asked to use the system for most of each day for assistance in walking. The stimulator was also used during PT sessions.

Assessment Protocol

The primary outcome measure was walking speed, which is a reliable measure that correlates well with more sophisticated methods of gait measurement.[27] It was recorded over a 10-m linoleum walkway; a walking aid was used, if required, but no other assistance was given and no orthoses were used. If a walking aid was needed, it was used at each assessment. A distance of 1m was allowed at both ends of the walkway for acceleration and deceleration. To achieve a consistent response, participants were instructed to walk briskly. Three consecutive measurements were taken for nonstimulated walking speed in both groups at each assessment. Similarly, stimulated walking speed was recorded in the treatment group after the baseline phase. In the treatment group, the order of recording while walking with and without stimulation was randomized to control for bias resulting from fatigue.

The Physiological Cost Index (PCI) is a measure of the energy efficiency of walking[28] and was recorded concurrently with walking speed. It describes the increase in heart rate, and therefore implied working oxygen consumption, in relation to walking speed. Thus,

$$\text{PCI} = \frac{\text{heart rate when walking} - \text{resting heart rate(beats/min)}}{\text{walking speed (m/min)}}$$

A Polar monitor[d] was used to record the minimum heart rate at rest and the maximum heart rate immediately after each 10-m walk. A reduction in the PCI represents an increase in gait efficiency.

The MAS[29] was scored as a clinical measure of spasticity with the patient supine, for the quadriceps femoris, hamstrings, and ankle plantarflexors and dorsiflexors.

The Rivermead Motor Assessment[30] (RMA) is an objective measure of function that gives a total score and 3 subsection scores: gross function, leg and trunk function, and arm function.

The Medical Outcomes Study 36-Item Short-Form Health Survey[31] (SF-36) was administered as an interview with the participants. It rates subjects on 8 dimensions of health: physical function, physical role, social function, emotional role, mental health, pain, energy, and general health.

Statistical Analysis

We used simple graphic plots of the control and treatment group response profiles over time. The statistical significance of observed changes within and differences between the group response profiles were assessed using standard linear regression test methods; that is, tests for significant trends in the median group responses against time and for common trends in both the control and treatment groups. Regression statistics make efficient use of the study data for test purposes, but they do not provide intuitively obvious measures of treatment effect sizes (eg, differences in mean walking speed at 12wk in milliseconds). To that end, we used analysis of covariance (AN-

Table 2: Demographic Data of the Participants at Week 4

	Control	Treatment
No. of subjects	8	10
Mean age ± standard deviation (y)	59.33±12.46	58.2±12.72
Age range (y)	44–78	41–78
Sex	4 men, 4 women	8 men, 2 women
Side of hemiplegia	4 right, 4 left	7 right, 3 left
Time since stroke (0–6mo)	3	6
Time since stroke (6–12mo)	5	4
Median time since stroke	195d (23.86wk)	167d (27.85wk)

COVA) to deliver baseline corrected estimates of means at 12 weeks, following the recommendations of Vickers and Altman.[32]

RESULTS

Thirty-two patients were screened for the study. Five patients did not meet the selection criteria and consent was not given by another 6. Twenty-one patients were recruited, 18 of whom completed the study. One control group participant withdrew after a subsequent stroke. One treatment group participant also withdrew after experiencing headaches that may have been associated with using stimulation; another was removed because that subject no longer fulfilled the selection criteria at week 0. Three participants experienced intercurrent illnesses that did not affect their ability to continue in the study: 1 participant in the treatment group fell and developed hearing and cardiac problems; 2 participants in the control group experienced minor health problems—1 had a lower back strain and the other had a seizure. For the purpose of power sampling, a total of 32 subjects had been suggested for the study, but this was not achieved within the time frame.

Differences between control and treatment groups with respect to the demographic variables listed in table 2 are consistent with random variation alone for this study's sample size (all $P>.10$). The most striking difference, time since stroke, was not significant (Fisher exact test, $P=.64$)

PT Sessions During the Study Period

The median number of PT sessions during the study period was 25.5 in the control group and 25 in the treatment group, which suggests that participants in both groups received a similar amount of PT intervention.

Changes During the Baseline Phase

There was no statistically significant change in median walking speed (primary outcome measure) for the control group ($P=.443$) or the treatment group ($P=.249$) during the baseline period (week −4 to week 0).

Graphic Representation of Data

Results of the outcome measures are presented using box and whisker plots, where the median value is given as a horizontal line with a numeric value, and the interquartile ranges are represented by the box. The whiskers show the extent of the range, with asterisks used to represent outlier values. Results are given for each assessment where the outcome measure was completed. One chart is given for the control group and 1 for the treatment group for each outcome measure. Two charts are given, however, for the results of walking speed and the PCI of gait in the treatment group, to illustrate data collected both without and with stimulation.

There was a statistically significant upward trend in walking speed for the control group ($P=.020$) and the treatment group (nonstimulated, $P=.004$; stimulated, $P=.042$). The difference in the location of the respective control and treatment group trend lines was also statistically significant (nonstimulated, $P=.040$; stimulated, $P=.009$). The ANCOVA adjusted mean walking speeds at 12 weeks were as follows: control group: .39m/s, and treatment group: nonstimulated, .43m/s; stimulated, .48m/s. The overall increase in walking speed relative to controls at 12 weeks was .04m/s (95% confidence interval [CI], .003–.090) without stimulation, and .09m/s (95% CI, .031–.150) with stimulation. The above increases in walking speed were larger than what was suggested by the median values recorded at 12 weeks in figures 2A, B, and C, reflecting the importance of ANCOVA in adjusting each subject's 12-week walking speed for his/her baseline speed.

A statistically significant downward trend in median PCI (fig 3) was observed for the treatment group (nonstimulated, $P=.007$; stimulated, $P=.020$), but not for the control group ($P=.292$). The difference in the location of the trend lines was statistically significant (nonstimulated, $P=.038$; stimulated, $P=.016$)

A statistically significant upward trend in median RMA total and gross scores (fig 4) was seen in the treatment group ($P=.024$, $P<.001$, respectively) but not in the control group ($P=.200$, $P>.200$, respectively). There were no statistically significant trends for the control group or treatment groups in the leg and trunk or arm sections of the RMA (all $P>.20$).

There were no statistically significant trends in any dimensions of the SF-36 in either control or treatment groups (fig 5).

There was an apparent downward, but nonstatistically significant, trend in median MAS (fig 6) of the ankle plantarflexors in the treatment group ($P=.282$). No trend was evident for the control group ($P=.742$). The difference at week 8 from baseline was statistically significant in the treatment group ($P=.022$).

There was an apparent, but nonstatistically significant, downward trend in the median MAS (fig 7) of the quadriceps femoris in the treatment group ($P=.051$). No trend was evident for the control group ($P>.20$). There was no statistically significant change in median MAS of the hamstrings in either the treatment group ($P=.326$) or the control group ($P=.553$). There was no change in median MAS of the dorsiflexors for either group, where the median score was 0, representing an absence of spasticity on clinical examination.

DISCUSSION

In this study, we observed patients within 1 year of stroke because we predicted that it is during this time that the combined intervention of FES and BTX would produce a clinically favorable response. However, it is normally accepted that not only does natural recovery occur mainly in the first year after stroke but also that spasticity develops during this time. (Stiffness developing later is probably due more to structural changes in the muscle that causes contractures rather than true, neurogenic spasticity.) Therefore, changes in spasticity (possible increase) and natural recovery (improvement in other outcome measures) may have been unrelated to the interventions, and baseline between-group differences may have biased the results. As expected in such a small study, there was a difference between the groups in time from stroke (median time: in treatment group, 28wk; in control group, 24wk). This difference favored an improvement due to natural recovery and an increase in spasticity in the control group—although, contrary

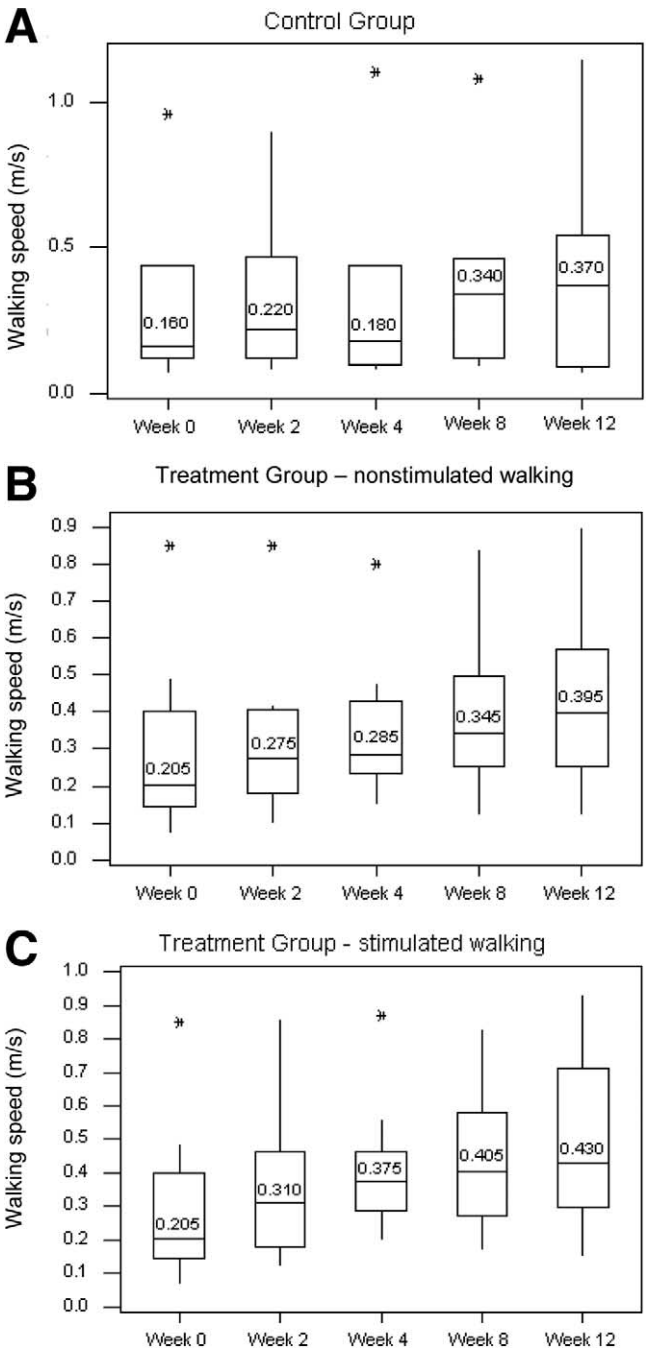


Fig 2. (A) Walking speed for the control group. (B) Nonstimulated walking speed for the treatment group. (C) Stimulated walking speed for the treatment group. Asterisks denote single outliers.

to expectation, spasticity of the ankle plantarflexors, measured by the MAS, was higher in the control group. Arguably, future studies could avoid these confounding variables by recruiting subjects who are more than 12 months from stroke, but clinically, the most effective time to use BTX may be as spasticity is developing rather than when secondary, biomechanic changes have occurred, as suggested by Burbaud et al.[20] Hesse[19] and Dunne[33] and colleagues, however, found that the effectiveness on BTX was not affected by chronicity.

Mobility and Function

The baseline adjusted rate of improvement in walking speed was statistically significantly greater in the treatment group than in the control group. Only in the treatment group was there a reduction in the effort of walking (PCI) and an improvement in functional mobility (RMA total and gross function scores). The upward but nonstatistically significant trend in the physical function dimension of the SF-36 was greater in the treatment group than in the control group, suggesting that improved

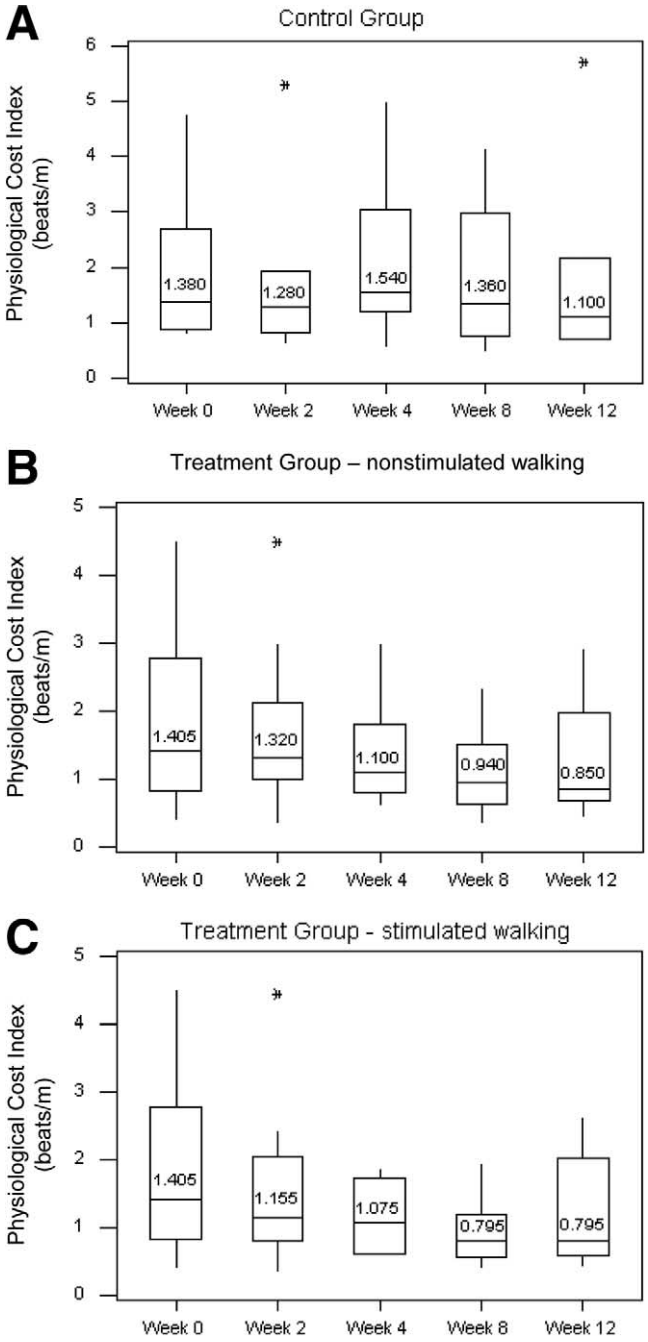


Fig 3. (A) The PCI of gait in the control group. (B) The PCI of nonstimulated walking in the treatment group. (C) The PCI of stimulated walking in the treatment group. Asterisks denote single outliers.

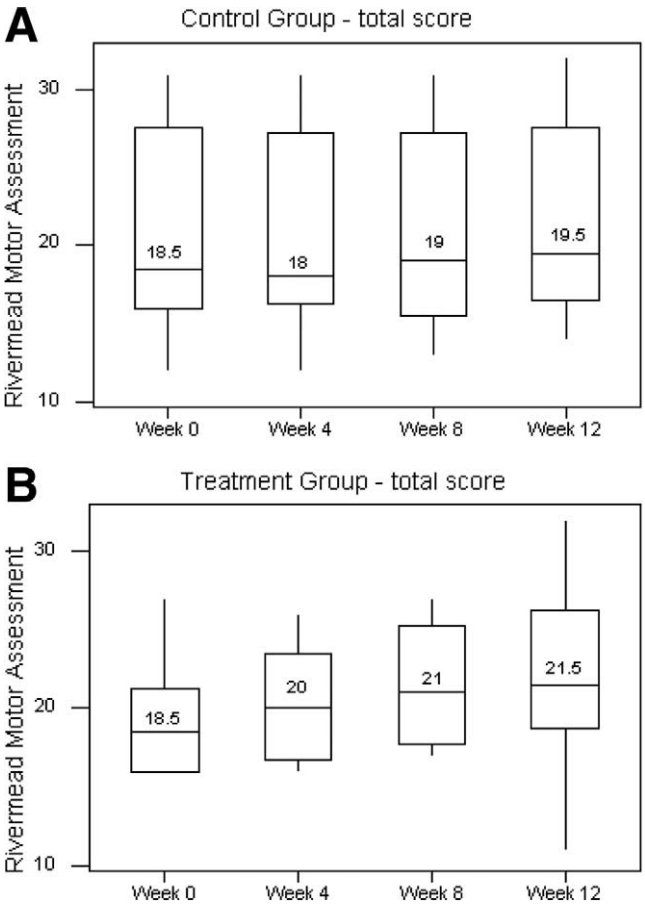


Fig 4. The RMA total score in (A) the control group and (B) the treatment group.

mobility in the treatment group may influence quality of life (QOL).

Comparing our results with the published data on changes in walking speed when BTX and FES were used singly to treat spastic drop foot in stroke, should be done with caution because of differences in our subjects' time since stroke; nevertheless, the following observations can be made.

Burbaud et al[20] reported a 17% increase in walking speed and Hesse et al[19] reported a 21% increase with BTX alone. In both studies mean time from stroke was just less than 2 years. Burridge,[11] Taylor,[12] and Wright[34] and colleagues all reported an increase in walking speed after a period of FES alone. Burridge[11] reported 13% over 12 weeks, and Taylor[12] reported 26% over 18 weeks. Wright,[34] in the only study of patients less than 12 months after stroke, reported a 58% increase after 12 weeks. In our study, a 109% increase was measured between baseline and week 12. Participants in these studies were not screened for calf spasticity; consequently, the value of direct comparisons is limited.

Spasticity

Results of the MAS showed a reduction in calf spasticity in the treatment group across the intervention phase. A statistically significant difference from week 0 was seen at week 8, when the effect of BTX would be expected to be greatest. It is also possible that the effect of FES may have enhanced the overall downward trend in spasticity through reciprocal inhibition of the antagonists.

The MAS for quadriceps femoris showed a reduction in spasticity over time in the treatment group. Burridge[11] showed this effect in chronic stroke patients using the ODFS and proposed that the reduction in extensor tone may be mediated through stimulation of the flexor withdrawal reflex. The findings here support the hypothesis that a reduction in extensor spasticity occurred with the combined treatment, where a decrease in both calf and quadriceps spasticity has been recorded. It is not possible to detect whether this effect is enhanced by the use of BTX or whether it is solely mediated through the use of FES. It may be that the use of BTX to decrease calf restraint may have an impact on extensor spasticity by reducing compensatory gait strategies, but this has not been reported in the literature.

Study Limitations and Further Work

The main weakness of the study design was that it is not possible to identify the contribution of the separate effects of BTX and FES. A 4-arm RCT is now needed to allow direct comparison of those effects and to gain further information on which to base clinical recommendations for treatment. Despite the difficulties with blinding the study, the primary outcome measure used was an objective measure, which strengthens the reliability of the data.

Individual response to the intervention varied, as can be seen from the large standard deviations (SDs), and may have been

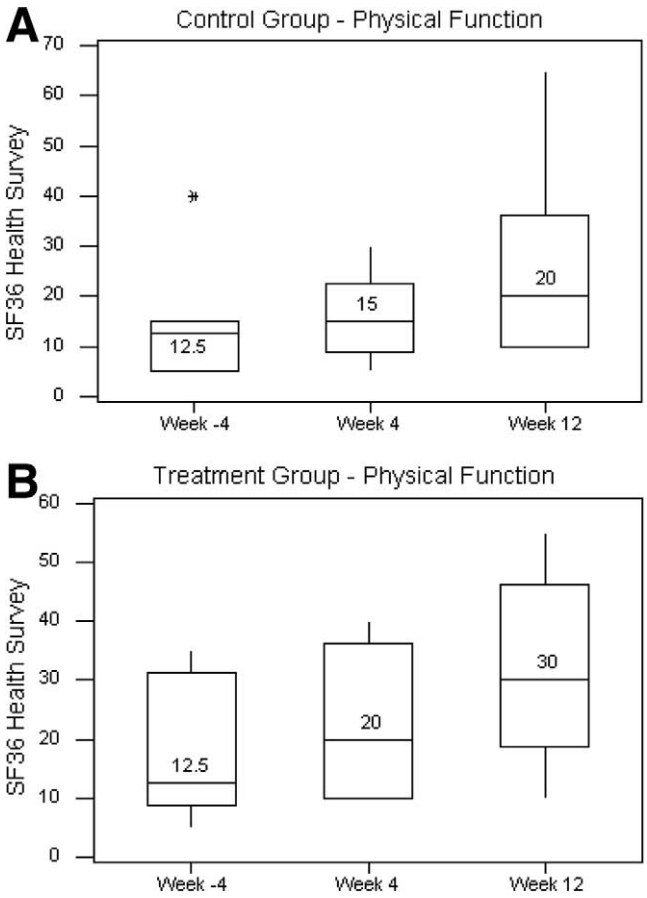


Fig 5. The SF-36 physical function dimension in (A) the control group and (B) the treatment group. Asterisk denotes single outlier.

related to severity of calf spasticity. Patients with premature calf activation, identified subjectively through the electromyographic recordings, were accepted into the study; an objective method of quantifying this might enable subjects to be more effectively screened.[26] A future study should stratify for spasticity at baseline and for mobility, either by score on the HAI or by walking speed.

Whether our findings support a further larger study must be addressed. In this preliminary study, we measured a small but statistically significant difference between the control and treatment groups in our primary outcome measure—walking speed. This represents a difference (regression adjusted median) of 9% between the treatment and control groups and, because it is generally accepted that an improvement of less that 10% is not clinically relevant, repeating the study with a larger sample is probably not justified. If, however, other studies were done, we would recommend that a more robust screening method be used to include only subjects with higher levels of calf spasticity and, because it is the long-term effect of the intervention that is of importance to the patients, that repeat injections of BTX be given and subjects followed up longer, preferably 26 weeks.

CONCLUSIONS

The study showed improvement in the walking speed of patients with a spastic drop foot treated with BTX and FES in combination. Small but consistent improvements were also measured across a range of outcomes, which suggests that the intervention may also improve function and QOL. A future study should be sufficiently powered to detect either a positive or negative effect statistically, and selection criteria, intervention, and follow-up should be considered to test for a clinically significant effect. The study has provided sufficient information on the variability of the primary outcome measure (walking speed) to facilitate sample size calculations for a subsequent study, to quantify the magnitude of the treatment effect (improvement in walking speed at 12wk) with a meaningful degree of precision. Using a 95% CI as a measure of precision and assuming a net gain in walking speed at 12 weeks of about 0.9m/s with a pooled SD of about .05m/s, the sample sizes required to keep the CI within ±.015, .025, or .025m/s of the estimated treatment effect would be 86, 50, and 30 subjects per group, respectively.

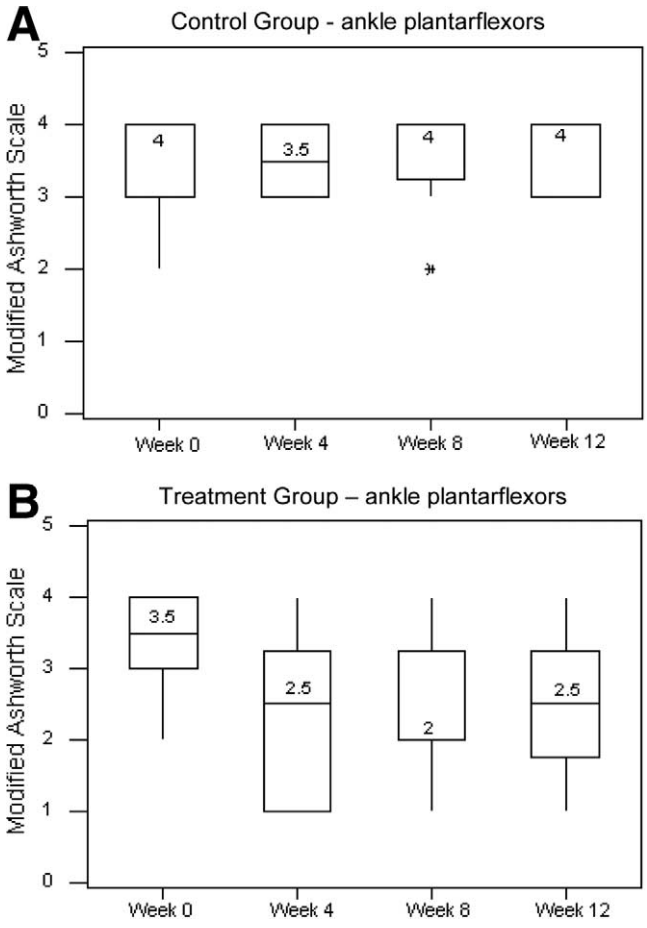


Fig 6. The MAS of the ankle plantarflexors in (A) the control group and (B) the treatment group. Asterisk denotes single outlier.

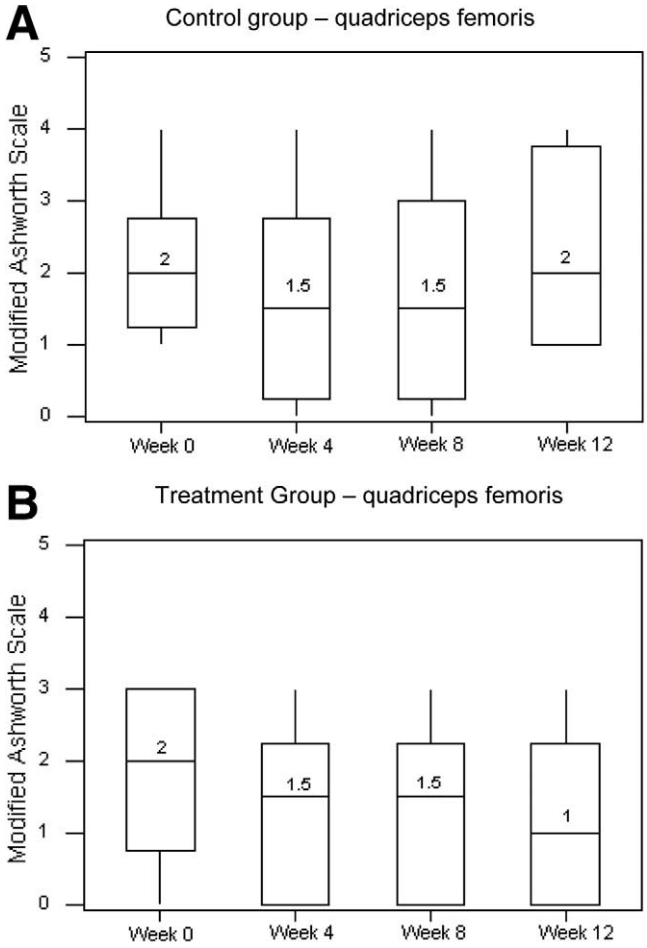


Fig 7. The MAS of the quadriceps femoris in (A) the control group and (B) the treatment group.

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