Combined effects of botulinum toxin and casting treatments on lower limb spasticity after stroke

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Summary

Optimal treatment of spasticity requires a combination of pharmacotherapy and muscle lengthening. We evaluated 13 stroke patients with equinovarus foot randomized to treatment with either botulinum toxin A (BTA) injection plus ankle-foot casting (n=6) or BTA alone (n=7). The tibialis posterior and calf muscles (range of BTA injection: 190 to 320 U) were treated in each patient. Castings were worn at night for four months. Each patient was examined before, and at two and four months after BTA injection using the static and dynamic baropodometric tests, the Modified Ashworth Scale and the 10-meter walking test. At two months, therapeutic effects were observed in both groups. At four months, the study group showed further clinical improvement, while the control group returned to baseline performance. Thus, prolonged stretching of spastic muscles after BTA injection affords long-lasting therapeutic benefit, enhancing the effects of the toxin alone.

KEY WORDS: ankle-foot casting, botulinum toxin, lower limb spasticity.

Introduction

Spasticity is classically defined as a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks (1,2). The main clinical problems related to spasticity of the lower limbs after stroke are a decrease in motility and the appearance of hypertonus, resulting in restrictions in the range of motion (ROM), abnormal postures, pain and occasionally fixed contracts, as well as reduced self-reliance and difficulties in activities of daily living (ADL) (3-5). The most common pathological posture, characteristic of superior motoneuron syndrome in lower limb spasticity (4,6), is equinovarus foot deformity in which the foot and ankle are bent in a plantar fashion and turned medially with curling of the toes. The muscles that contribute to this pathological posture are the tibialis posterior (TP), gastrocnemius lateralis (GL) and medialis (GM), and soleus (Sol). Overactivity of these muscles produces ankle inversion, moving the heel into an equinovarus position; this hinders adequate pronation and shifts the body weight onto the lateral support of the foot (7), causing both pain and instability. For this reason it is very important to initiate an early, appropriate rehabilitation program that preserves muscle viscosity and flexibility, avoiding fixed contracts and abnormal postures. It has been reported that more satisfactory results are obtained if physiotherapy is combined with antispastic medications (4). However, both systemic antispastic medications and more invasive approaches, such as alcoholic neurolysis or even orthopedic surgery, offer limited therapeutic benefit (8).

Several investigators have suggested that treatment with botulinum toxin type A (BTA) for upper or lower limb spasticity is both efficacious and safe (1,3,6,9,10). However, given the high cost of BTA, the relatively short duration of the clinical improvement it gives, and the subsequent need for higher doses to achieve significant tone reduction, alternative strategies have been explored in order to improve the cost-benefit ratio. Reiter et al. (4) have shown that combined treatment for spastic foot using selective injections of BTA followed by ankle-foot taping for a period of three weeks is as effective as injection of the spastic muscle and reduction of foot inversion, although the benefit was longer-lasting in the combined treatment group.

The rationale for combining BTA with muscle lengthening treatment is based on the assumption that muscle shortening increases spindle sensitivity and spasticity (11); combining muscle chemodenervation with lengthening procedures should maximize the potential for inhibition of muscle hyperactivity (12). In order to determine the effectiveness of muscle lengthening after BTA injection, we applied a protocol, involving a new casting procedure, in sub-acute or chronic stroke patients with lower limb spasticity during rehabilitation. We then compared the effectiveness of a rigid ankle-foot cast worn (only at night) for four months after BTA injection with BTA injection alone in reducing lower limb spasticity.
Materials and methods

Patients

Twenty patients who had suffered a first cerebrovascular stroke were recruited from the neurorehabilitation outpatients department of the Functional Reeducation Center at the G.B. Rossi Hospital in Verona in the period from January to August 2006. The time since onset of the cerebrovascular event ranged from six months to two years. Inclusion criteria were:

– the presence of equinovarus foot due to severe lower limb spasticity, corresponding to at least grade 3 on the modified Ashworth Scale (13) at calf muscles;
– impaired walking and ADL;
– the ability to walk for at least 10 meters with or without aid;
– written informed consent to treatment for spastic foot using BTA injection followed by ankle casting;
– a mean score on the European Stroke Scale (ESS) (14) ≥ 43/100; and
– a Barthel Index (BI) (15) ≥ 55/100.

Exclusion criteria were treatment with oral antispastic medications during the four weeks prior to recruitment, previous treatment with BTA, severe fixed contractures impairing mobility, and a history of allergy.

After clinical history taking, four patients were excluded (two had taken antispastic drugs and two had undergone BTA injection during the previous month). A further three of the recruited patients were not available for follow-up examinations. Thus, 13 patients (9 with right and 4 with left hemiparesis) were included in the study. Using a simple randomization procedure, six patients were included in the study group (treatment with BTA plus casting at night) and seven in the control group (treatment with BTA alone) (Table I).

Treatment procedures

BTA injection. All the patients received an electromyography (EMG)-guided injection of 190 to 320 U of BTA (BOTOX), diluted with saline to a concentration of 5 U/0.1 mL, in the following muscles: TP, Sol, GM, and GL. The medication was injected in two sites per muscle. The selection of the muscles to be treated took into account both limb posture and EMG activity monitoring findings.

Casting procedure. As from 10 days after BTA injection, the patients in the study group wore rigid night-time made-to-measure ankle foot orthoses for four consecutive months in order to keep the talocrural joint at maximum dorsiflexion (approximately 90°) and achieve extension passively without crossing the pain threshold. For this purpose, Neofrakt® (Beek, Belgium) static leg orthoses were used, which can be molded directly to the patient’s body according to the shape of the parts that need to be immobilized. These casts are made of two stiff polyurethane foam shells with an outer layer in textile fiber. They are removable by means of two lateral zips and can be worn many times before having to be remolded. X-ray transparent, waterproof and washable, they are three to four times lighter than plaster casts. The time required to prepare a cast was about 15 minutes. All the patients received two half-hour instruction sessions on the correct use of the casts.

Evaluation procedure

Each patient was always examined by the same investigator before (T0), and at two (T1) and four (T2) months after BTA injection. The investigator was blinded to the treatment the patient was receiving.

Table I. Socio-demographic and clinical features of patient groups.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>ESS</th>
<th>BI</th>
<th>Affected side</th>
<th>Duration of stroke (mths)</th>
<th>Total dose (Botox units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>M</td>
<td>66</td>
<td>80</td>
<td>Right</td>
<td>18</td>
<td>280</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>M</td>
<td>72</td>
<td>70</td>
<td>Left</td>
<td>22</td>
<td>300</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>F</td>
<td>58</td>
<td>55</td>
<td>Right</td>
<td>8</td>
<td>300</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>M</td>
<td>73</td>
<td>70</td>
<td>Right</td>
<td>13</td>
<td>300</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>M</td>
<td>43</td>
<td>65</td>
<td>Right</td>
<td>21</td>
<td>290</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>F</td>
<td>66</td>
<td>70</td>
<td>Right</td>
<td>19</td>
<td>300</td>
</tr>
<tr>
<td>Mean</td>
<td>62</td>
<td>63</td>
<td>68.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>±11.83</td>
<td>±11.17</td>
<td>±8.16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Control group |
| 7 | 70 | F | 58 | 70 | Right | 7 | 300 |
| 8 | 65 | F | 54 | 55 | Right | 10 | 280 |
| 9 | 72 | F | 66 | 60 | Right | 20 | 300 |
| 10 | 60 | F | 66 | 65 | Left | 12 | 300 |
| 11 | 70 | M | 58 | 70 | Right | 17 | 280 |
| 12 | 59 | M | 60 | 60 | Left | 23 | 300 |
| 13 | 63 | M | 62 | 65 | Left | 18 | 280 |
| Mean | 65.6 | 60.57 | 63.6 |
| SD | ±5.2 | ±4.43 | ±5.56 |

Abbreviations: ESS = European Stroke Scale; BI = Barthel Index.
The following tests were used:

i) **Baropodometry.** Baropodometric tests were carried out using a footboard that had two sensors per cm² and an effective measurement area of 27.4×48.8 cm. Inputs from the footboard are transduced by means of software that yields data regarding weight distribution and area of foot support in static and dynamic conditions.

All patients were examined barefoot in a comfortable environment. During the static baropodometric test the patient was required to maintain the standing position in the middle of the footboard for 10 seconds. The average footprint area of the affected foot was measured. Instead, the dynamic baropodometric test records the support areas at 25%, 50%, and 75% of step while the patient takes one step with the affected foot on the footboard. The total full-load time was also recorded. Five patients used a cane in the dynamic test, and only one in the static test.

ii) **Modified Ashworth Scale.** Patients were tested during passive ankle dorsiflexion in a supine position in order to evaluate spasticity of the calf muscles (score: 0-4).

iii) **10-meter walking test.** Patients were asked to walk 10 meters independently at maximum speed in their usual shoes, without any casting or semi-rigid ankle-foot orthoses to support the tibiotarsal joint. Five patients walked with a cane. The time taken to walk 10 meters was measured with a stopwatch.

### Statistical analysis

Statistical analysis was performed using parametric tests. Homogeneity of group demographic and clinical data was tested using the independent sample t-test. Changes in performance in each group for each outcome measure were analyzed by analysis of variance (ANOVA) for repeated measures, comparing data recorded before (T0), and at two (T1) and four (T2) months after BTA injection. Post-hoc comparisons between T0 and T1 and between T0 and T2 were carried out using the dependent samples t-test. The independent samples t-test was used to compare the effects of treatment in the study and control groups. In the case of multiple comparisons the Bonferroni adjustment was applied. The alpha level for significance for all analyses was set at p<0.05.

### Results

The independent sample t-test showed that there were no significant differences between the two groups (p>0.05) as regards age, time from stroke, neurological severity measured with the ESS and autonomy in daily life measured with the BI, before treatment (T0).

**Within-group treatment effects**

Study group. General statistical analysis with ANOVA for repeated measures showed significant changes from baseline in all outcome measures (static baropodometric test: average area (F=10.782, df 2, p<0.05); dynamic baropodometric test: support areas at 25% (F=24.151, df 2, p<0.01), 50% (F=104.286, df 2, p<0.01), and 75% of step (F=39.805, df 2, p<0.01), total full-load time (F=23.587, df 2, p<0.01); Ashworth Scale (F=4.333, df 2, p<0.05]), with the sole exception of the 10-meter walking test.

Post-hoc comparisons using the paired-samples t-test showed significant improvements two months after treatment (T0 vs T1) in average area, support areas at 25%, 50%, and 75% of step (p<0.05), total full-load time, and Ashworth Scale. These improvements persisted at the follow up four months after the toxin injection (T0 vs T2) in all evaluation tests except for the average footprint area of the affected foot in the static baropodometric test (Fig.s 1, 2 and 3).
Control group. General statistical analysis with the ANOVA parametric test showed significant changes from baseline in the following evaluation tests in all patients tested [static baropodometric test: average area (F=10.953, df 2, p<0.05); dynamic baropodometric test: support areas at 25% (F=16.682, df 2, p<0.01), 50% (F=13.363, df 2, p<0.05), and 75% of step (F=39.386, df 2, p<0.01), total full-load time (F=4.922, df 2, p<0.05); Ashworth Scale (F=5.083, df 2, p<0.05)]. Significant changes were not observed in the 10-meter walking test. Post-hoc comparisons using the paired-samples t-test showed a significant improvement two months after treatment (T0 vs T1) in support areas at 25%, 50%, and 75% of step (p<0.05). These improvements were not seen at four months (T0 vs T2) in any of the evaluation tests. The post-hoc comparisons showed no significant changes after treatment in Ashworth Scale scores (p=0.140), average area (p=0.242), and total full-load time (p=0.707) (Fig.1, 2 and 3).

**Between-groups treatment effects**

Analysis with the independent samples t-test showed that the effects of treatment differed significantly between the study and control groups only with regard to the T2-T0 differences in the support areas at 25%, 50%, and 75% of step (df 11, p<0.01), the Ashworth Scale (df 11, p<0.05), average area (df 11, p<0.05), and total full-load time (df 11, p<0.01). No significant differences were observed in the 10-meter walking test at any time (Table II).

**Discussion**

This study is the first randomized controlled study to evaluate the combined effects of a made-to-measure cast (worn at night) and botulinum toxin injection in the treatment of equinovarus foot after stroke. The results demonstrate that prolonged stretching of spastic muscles, obtained by means of casting, after BTA injection gives a longer-lasting therapeutic benefit compared to BTA injection alone, as assessed by the Modified Ashworth Scale, and by static and dynamic baropodometric tests.

The main limitation of the procedure proposed in this study is the need for good patient compliance in order to ensure regular use of the cast. Serial plaster casts have long been used as an adjunct to physiotherapy in the management of children with cerebral palsy (16). They have also been used in adults with acquired brain injury to achieve a variety of therapeutic aims. The rationale for the use of serial ankle castings is to increase joint ROM and muscle extensibility, thereby improving functional alignment and biomechanics during weight-bearing tasks (17).

Another common procedure in the treatment of gait disorders secondary to equinovarus foot deformity is BTA injection (3,6). The effects of this procedure, however, are relatively short-lasting in spasticity (5,6,8,10).

Flett et al., in a recent study (18), compared BTA injection with fixed plaster cast stretching for dynamic calf tightness in the management of spasticity in children with cerebral palsy. Their results showed that the two treatments had comparable effects. However, parents consistently favored BTA and stressed the inconvenience of serial plaster casting.

Other studies have compared the effects of casting plus BTA injection with those of the standard BTA procedure. Reiter et al. (4) have shown that the combined use of low-dose botulinum toxin and ankle taping in spastic equinovarus foot after stroke improves foot position at rest and passive ankle ROM, as well as having positive effects on gait parameters. The taping procedure, however, needs to be carried out by an expert operator and repeated many times. Furthermore, taping limits the patient’s daily personal hygiene for a considerable period. All these results are confirmed by the present study. However, there emerge many aspects in favor of the casting proposed in the present study in comparison with other joint positioning procedures. The plaster cast can be worn many times before having to be re-molded; it can easily be removed by means of two lateral zips with the aid of a caregiver; it can be worn only at night, leaving the patient’s foot free during the daytime, and it is well tolerated, causing the patient only minor discomfort. On the basis of these observations we may reasonably hypothesize that this procedure may be used for extended periods in patients with stroke for prolonged maintenance of calf muscle lengthening and prevention of ankle-foot secondary damage.

As for the mechanisms responsible for the functional effects of the casting, a number of hypotheses can be put forward. First, the cast enables the patient’s affected foot to be positioned in such a way as to maintain prolonged stretching of the most spastic muscles (triceps surae, extrinsic toe flexors). It is known that prolonged stretching can inhibit muscle spasticity (19) and thus may enhance the effects of other pharmacological treat-

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**Table II. Differences (T1-T0 and T2-T0) in all outcome measures in study and control group.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Ashworth Scale</th>
<th>Average area</th>
<th>Full load</th>
<th>25% support area</th>
<th>50% support area</th>
<th>75% support area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>Mean SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-T0</td>
<td>-0.41 ±0.34</td>
<td>9.61 ±4.52</td>
<td>14.53 ±5.42</td>
<td>366.66 ±250.57</td>
<td>636.66 ±285.28</td>
<td>7.66 ±4.84</td>
</tr>
<tr>
<td>Study</td>
<td>Mean SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>T2-T0</td>
<td>-0.58 ±0.34</td>
<td>6.80 ±7.95</td>
<td>7.33 ±5.11</td>
<td>112.86 ±209.74</td>
<td>142.86 ±181.16</td>
<td>7.46 ±6.45</td>
</tr>
<tr>
<td>Control</td>
<td>Mean SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-T0</td>
<td>-0.21 ±0.247</td>
<td>6.085 ±7.104</td>
<td>-7.33 ±7.95</td>
<td>129.74 ±181.16</td>
<td>142.86 ±181.16</td>
<td>7.46 ±6.45</td>
</tr>
<tr>
<td>Control</td>
<td>Mean SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2-T0</td>
<td>0.428 ±0.495</td>
<td>6.085 ±7.104</td>
<td>7.33 ±5.11</td>
<td>112.86 ±209.74</td>
<td>142.86 ±181.16</td>
<td>7.46 ±6.45</td>
</tr>
</tbody>
</table>

Abbreviations: T0=before BTA injection; T1= two months after BTA injection; T2= four months after BTA injection.
Effects of casting and botulinum toxin on lower limb spasticity

...ments for spasticity. Short-term stretching procedures obviously produce only short-lasting effects (20). In view of this, the casting procedure proposed in this study—the cast is worn for many hours during the night—may result in longer-lasting inhibition of spasticity (21). Second, this method is capable of changing the mechanical properties of the muscle and other soft-tissue structures, resulting in their elongation (22).

It is known that changes in the proportion and organization of intramuscular connective tissue; associated with immobility following brain injury, begin to manifest themselves clearly within a few weeks (23). During this time the number of sarcomeres in series of the muscle decreases and this produces a fixed contracture (24). The results of the evaluation procedure used in our study, based on static and dynamic baropodometric tests, show an improvement in the patients in the study group, an improvement clearly reflected in all the outcome measures except for the 10-meter walking test. Nevertheless, all the patients treated with BTA plus casting showed a reduction in the time taken to walk 10 meters at two (T1) and four months (T2) after treatment. The fact that this improvement lacked statistical significance may be attributable to the fact that the test is not sensitive enough to detect discrete changes in walking impairment. A reliable demonstration of significant improvement in walking may require, in addition to casting after BTA injection, rehabilitation training that resets the step sequence in terms of cadence, stride length, stance (affected vs non-affected foot) and swing time (affected vs non-affected) symmetry and double stance duration as a percentage of cycle duration (3).

Finally, in the future, other studies will be needed to assess the possibility of reducing the total dose administered, to prevent the development of antibodies that has been reported after the use of high doses during chronic treatment (25), and of reducing the effective cost compared to the current approach. Moreover, it might also be interesting to determine whether the chronic use of casts during the night-time can reduce, from year to year, the number of BTA injections needed.

In conclusion, the results of this study show that the combination of BTA injection and casting treatment at night for lower limb spasticity after stroke is effective, non-invasive, inexpensive, and well accepted by patients.

References


