Review Article

Botulinum Toxin for Post-stroke Spastic Hypertonia: A Review of its Efficacy and Application in Clinical Practice

Gerard E Francisco,[1,2] *MD*

Abstract

Botulinum toxins (BTX) have revolutionised the management of focal post-stroke spastic hypertonia. Published literature has supported the efficacy and safety of BTX in reducing spastic hypertonia but has not convincingly demonstrated the ability to enhance function. While clinicians and stroke survivors have reported impressive clinical outcomes, randomised, controlled trials (RCTs), have demonstrated only significant improvement in muscle tone but not functional changes. This paper will review the evidence supporting the efficacy of BTX for spastic hypertonia and discuss current clinical practice.

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Key words: Botulinum toxins, Cerebrovascular accident, Spasticity, Stroke

Introduction

Botulinum toxins (BTX) have revolutionised the management of focal spastic hypertonia in a variety of neurologic diseases. Prior to the introduction of BTX for this purpose in the early 1990s, clinicians were limited to oral spasmolytic agents and nerve blocks using phenol or alcohol. All these interventions are effective in controlling spasticity, but side effect profiles vary. Oral drugs lack treatment target specificity and are associated with a multitude of adverse events, such as drowsiness and sedation. Phenol and alcohol require expertise in technique and are, like BTX, desirable for focal intervention. However, they have associated complications, such as swelling and dysaesthesia. Due to its relative effectiveness and safety compared to other spasmolytic options, the popularity of BTX in the management of spastic hypertonia has grown significantly over the last 2 decades. The literature has supported the effectiveness of BTX in reducing hypertonia but has not convincingly demonstrated functional improvement. While both clinicians and patients report impressive clinical outcomes, this has not been reflected in randomised, controlled trials (RCTs). This paper will review the evidence supporting the efficacy of BTX for spastic hypertonia and discuss current clinical practice.

An online literature search was performed in May 2006, using Medline and PubMed. Search terms used were "stroke", "cerebrovascular accident", "spasticity", and "botulinum toxins". The search yielded a total of 140 articles, but only 8 RCTs were found and included in this review.

The majority of papers investigated the effects of BTX on upper limb spastic hypertonia only. Five studies reported the outcomes of BTX therapy in decreasing hypertonia in various upper limb muscles, mostly involving the elbow, finger and wrist flexors.

Evidence of Efficacy of Botulinum Toxin Type A (BTX-A)

Upper Limb

Simpson[1] published the first RCT of BTX-A for upper limb post-stroke spastic hypertonia. Thirty-nine subjects were randomised into 1 of 4 groups. Each subject received either saline (placebo) or 1 of 3 total doses of Botox® (Allergan, Inc., Irvine, CA): 75 u, 150 u, or 300 u divided between the biceps, flexor carpi radialis (FCR) and flexor carpi ulnaris (FCU). The group that showed most significant improvement in hypertonia reduction in the elbow and wrist flexor at 2, 4 and 6 weeks post-injection, as measured by the Ashworth Scale (AS) was the group that received the highest dose. At 6 weeks, the AS scores for the wrist and

[1] Vice-Chairman and Clinical Associate Professor
Department of Physical Medicine and Rehabilitation, University of Texas Health Science Center, USA
[2] Interim Co-Director, Brain Injury and Stroke Program, Outpatient and Research Services
Memorial Hermann-The Institute for Rehabilitation and Research (TIRR), Houston, Texas, USA
Address for Correspondence: A/Prof Gerard E Francisco, 1333 Moursund Avenue, Houston, TX 77030, USA.
Email: Gerard.E.Francisco@uth.tmc.edu

elbow flexors decreased by 1.2 ± 1.2 (P = 0.026) and 1.1 ± 0.9 (P = 0.199) points, respectively. AS scores returned to pre-injection levels at week 16. No drug-related adverse event was reported.

Brashear et al[2] investigated the efficacy of Botox® in the treatment of wrist and finger flexor spastic hypertonia. This RCT is, thus far, the largest on the use of BTX-A in spastic hypertonia. Although the wrist and finger flexors were the primary foci of treatment, investigators were given the option to inject 40 u of Botox® to the thumb flexor if clinically indicated. One hundred and twenty-six subjects were randomised into 2 groups. The clinical responses of the 64 subjects who received 200 to 240 u of Botox® were compared to those who were injected with placebo (n = 62) over a 12-week period. The Botox® group had superior improvement of muscle tone as measured by the AS scores at 4, 6, 8 and 12 weeks. Moreover, at week 6, 62% in the BTX group, as opposed to 27% in the placebo group, reported improvement of at least 1 point on the Disability Assessment Scale (DAS) in the principal target of treatment (P <0.001) (The DAS is a measure of changes in various impairment and functional domains, including pain, deformity, hygiene and orthotic fit). No major adverse event was reported.

A more recent study that involved 91 stroke survivors using BTX-A to treat wrist and elbow flexor spastic hypertonia showed similar beneficial effects of BTX-A in decreasing upper limb flexor spasticity.[3] The subjects were randomised into one of the following groups: placebo, 90 u, 120 u and 360 u of Botox®, and were injected in the elbow, wrist and finger flexors. While all those injected with Botox® demonstrated improvement in modified Ashworth Scale (MAS) scores (P <0.05), the group that received the highest dose also showed the most improvement, a finding that is consistent with Simpson et al's observation.[1] At week 12, about 57% of the subjects who had a MAS score of ≥2 in either elbow or wrist flexors were re-injected with BTX-A. At week 18, 14 of 16 subjects who received 360 u responded, as compared to only 6 of 17 who received placebo (P = 0.004). Although improvements were observed, there was no strong dose-response relationship.

Results with Dysport® (Ipsen, UK), another preparation of BTX-A, have been similar. Bakheit et al[3] published the results of a dose-ranging study involving 83 participants, who were assigned to either placebo or 1 of 3 Dysport® dose groups (500 u, 1000 u, 1500 u). Muscles injected were the biceps, FCR, FCU, flexor digitorum superficialis (FDS), and the flexor digitorum profundus (FDP). All 3 Dysport® groups demonstrated significant improvement in modified AS (MAS) scores, but weakness was observed in the 1500 u group. Thus, the study suggests that the optimal dose may be 1000 u.

Another study compared placebo with Dysport® 500 u, 1000 u, and 1500 u in treating spastic hypertonia of the biceps, wrist flexors, finger flexors, and thumb adductors or flexors due to either stroke or TBI.[4] When doses were combined, there was a significant reduction of MAS scores in the wrist and finger flexors at 6 weeks post-injection (P <0.01), but this effect did not persist at 12 weeks. However, when individual dose groups were compared, there was no significant difference between groups at 6 weeks, except for improved AS scores in the elbow and wrist flexors (P <0.05) and passive range of motion (PROM) at the elbow (P <0.02). Consistent with Bakheit et al's findings, the group that received higher doses had greater hypertonia reduction than placebo, but did not have an advantage in terms of duration of effect.

In another investigation, 59 subjects were randomised to receive either placebo (n = 32) or 1000 u of Dysport® (n = 27) divided between the biceps, FCR, FCU, FDS, and FDP.[5] At the primary assessment endpoint at 4 weeks post-injection, the Dysport® group had a more significant improvement in MAS scores as compared to placebo (P = 0.004).

Lower Limb

An investigation of 23 stroke survivors showed that injection of a total of 1000 u to various lower limb muscles, including the gastrocnemius, soleus, tibialis posterior and flexor digitorum longus, was significantly better than placebo in improving AS scores in the ankle plantar flexors (P <0.0002) and invertors (P = 0.0002).[6] Pittock et al[7] reported that Dysport® injected to both heads of the gastrocnemius and soleus was superior to placebo in decreasing muscle tone, and that higher doses resulted in more significant changes (P = 0.0002). Two hundred and thirty-four subjects were randomised into 4 groups: placebo, or 1 of 3 total doses of Dysport® (500 u, 1000 u or 1500 u). While the primary measures, namely the 2-minute walking distance and stepping rate, increased significantly in each group (P <0.05), there was no significant difference between all groups, including placebo. Similar to previous findings, the most significant improvement in spasticity was in the group that received the highest dose (1500 u) (Table 1).

In summary, studies using 2 preparations of BTX-A have demonstrated significant efficacy in decreasing spastic hypertonia (as measured by the AS or MAS) of upper and lower limb muscles. The effect of BTX on function, however, has not been systematically investigated. Although some studies[2,4,9] attempted to look at functionality of the upper limb (e.g., changes in hygiene and use of orthosis; decrease in caregiver burden), none have addressed changes in active use of the upper limb. The same is true for lower limb studies, which primarily assessed muscle tone

Table 1. Evidence Summary: Randomised, Controlled Trials

<table>
<tr><th>Author (year)</th><th>Subjects</th><th>Intervention</th><th>Main Outcome Measure(s)</th><th>Results</th><th>Comments</th></tr>
<tr><td colspan="6">Botox™</td></tr>
<tr><td>Simpson et al (1996)[1]</td><td>n = 39; ≥9 mo post-stroke (mean = 3 y);Average MAS ≥2.5 inelbow and wrist flexors</td><td>Compared 3 total doses of Botox™ to placebo injected to BB, FCR, FCU, or placebo:
Low – 75 u total
Medium – 150 u total
High – 300 u total</td><td>MAS</td><td>Improvement in elbow and wrist flexor MAS scores in high dose (HD; 300 u) group at 2, 4 and 6 wks post-injection compared to placebo (P; P <0.05)
<table><tr><th rowspan="2">Wk</th><th colspan="2">MAS change Elbow flexor</th><th colspan="2">MAS change Wrist flexor</th></tr><tr><th>P</th><th>HD</th><th>P</th><th>HD</th></tr><tr><td>2</td><td>0.3</td><td>1.4</td><td>0.3</td><td>1.4</td></tr><tr><td>4</td><td>0.3</td><td>1.4</td><td>0.2</td><td>1.5</td></tr><tr><td>6</td><td>0.6</td><td>1.5</td><td>0</td><td>1.4</td></tr></table>MAS returned to near-baseline scores by wk 16 post-injection</td><td>No significant difference between placebo and treatment groups on other impairment and functional measures (FIM; FM; caregiver dependency; function and pain assessment; motor/function task rating scale)</td></tr>
<tr><td>Brashear et al (2002)[2]</td><td>n = 126; ≥6 mo post-stroke; AS ≥3 in wrist flexors and AS ≥2 in finger flexors; DAS≥2</td><td>Injected Botox™ to FCR, FCU, FDS, FDP ± FPL/FPB (total 200 to 240 u) or placebo</td><td>AS; DAS</td><td>Improvement in DAS scores in BTX group compared to placebo (P) at 4 and 6 wks (P ≤0.001) and 8 and 12 wks (P = 0.03):
<table><tr><th>Wk</th><th colspan="3">Change in DAS Scores</th></tr><tr><td></td><td>P</td><td>BTX</td><td>P value</td></tr><tr><td>6</td><td>-0.31</td><td>-0.94</td><td><0.001</td></tr><tr><td>12</td><td>-0.46</td><td>-0.88</td><td>0.02</td></tr></table>Improvement in wrist and finger, and thumb flexor AS scores at 4, 6, 8, and 12 wks post-injection:
<table><tr><th colspan="4">Change in AS Scores</th></tr><tr><td></td><td>P</td><td>BTX</td><td>P value</td></tr><tr><td>Wrist Flexors</td><td></td><td></td><td></td></tr><tr><td>Wk 6</td><td>-0.48</td><td>-1.66</td><td><0.001</td></tr><tr><td>Wk 12</td><td>-0.31</td><td>-1.07</td><td><0.001</td></tr><tr><td>Finger Flexors</td><td></td><td></td><td></td></tr><tr><td>Wk 6</td><td>-0.32</td><td>-1.34</td><td><0.001</td></tr><tr><td>Wk 12</td><td>-0.12</td><td>-0.378</td><td><0.001</td></tr><tr><td>Thumb Flexors</td><td></td><td></td><td></td></tr><tr><td>Wk 6</td><td>-0.62</td><td>-1.31</td><td>0.09</td></tr><tr><td>Wk 12</td><td>-0.31</td><td>-0.92</td><td>0.02</td></tr></table></td><td>DAS was meant to measure one target “functional disability” (hygiene, dressing, limb position, pain)</td></tr>
</table>

Table 1. Contd.

<table>
<tr><th>Author (year)</th><th>Subjects</th><th>Intervention</th><th>Main Outcome Measure(s)</th><th>Results</th><th>Comments</th></tr>
<tr><td>Childers et al (2004)[3]</td><td>n = 91; ≥6 wk post-stroke (mean 25.8 mo; range 0.9 to 226.9 mo); MAS ≥3 in wrist flexor and MAS ≥2 in elbow flexor</td><td>Up to 2 injections with either placebo or Botox™ (90 u, 180 u, 360 u total) to elbow, wrist, and finger flexors

Concurrent PT or splinting allowed but not changed during study participation</td><td>MAS</td><td>Improvement in elbow, wrist and finger flexor MAS scores at various wks post-injection in Botox groups compared to placebo (P <0.05):

Wk — Change in DAS Scores of wrist flexors (primary outcome measure)
P | BTX 360 u | P value
3 | -0.6 | -1.5 | <0.001
6 | -0.7 | -1.6 | <0.001
9 | -0.6 | -1.4 | <0.05

Similar improvement in MAS scores after repeated Botox™ injection

Dose-response pattern in MAS, but not FIM, global assessment, or SF-36 Health Survey</td><td>Wide range of stroke duration may have affected outcome

First study to show effect of repeated Botox™ injection in a blinded manner

14 subjects (15.3%) did not complete study (first injection)</td></tr>
<tr><td>Dysport™</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Bakheit et al (2000)[8]</td><td>n = 83; ≥3 mo post-stroke; MAS ≥2 in elbow, wrist, and finger flexors</td><td>Injected placebo or Dysport™ to BB, FCR, FCU, FDS, FDP: (500 u, 1000 u, or 1500 u total)</td><td>MAS</td><td>Improvement in summed MAS scores (elbow + wrist + finger flexors) at 4 wks post-injection in Dysport™ groups compared to placebo (P <0.05):

Summary of Best Change in Summed MAS Scores at 4 wks Post-injection and Odds Ratio for Improvement in Dysport® Groups as Compared to Placebo (P)
MAS score change from baseline | P | 500 u | 1000 u | 1500 u
-4 | 0 | 0 | 1 | 2
-3 | 0 | 4 | 7 | 4
-2 | 6 | 11 | 8 | 4
-1 | 7 | 5 | 4 | 5
0 | 6 | 2 | 1 | 4
1 | 0 | 0 | 1 | 0
Odds Ratio | | 0.246 | 0.134 | 0.245

No statistically significant improvement in active and passive ROM, pain, Barthel Index, MAS, and specific functional activities (cleaning palm of hand, cutting fingernails, putting arm through sleeve)</td><td>Optimal dose in those with residual voluntary upper limb movement is 1000 u</td></tr>
</table>

Table 1. Contd.

Author (year)	Subjects	Intervention	Main Outcome Measure(s)	Results	Comments
Smith et al (2000)[4]	n = 21 (19 stroke, 2 head injury), with "troublesome spasticity" in the upper limb; ≥1 y post-stroke	Injected placebo or Dysport™ (500 u, 1000 u or 1500 u total) 2/3 of total dose allotted to "above elbow" muscles, and 1/3 to "below elbow" muscles (divided equally between wrist and finger flexors)	MAS; PROM/ AROM; FAT	Improvement in wrist and finger flexor MAS (P <0.01) and wrist PROM (P = 0.05) at 6 wks in combined treatment groups compared to placebo Group — Mean change in MAS Scores at 6 wks post-injection Elbow flexor / Wrist flexor / Finger flexor Placebo: 1 / 0 / 2 500 u: -1 / -1* / -3 1000 u: -2 / -2 / 0 1500 u: -1† / -2† / -1† Combined: -1 / -2‡ / -2‡ *P <0.05; †P <0.01; ‡P = 0.06 No significant change in AROM and FAT	Mixed diagnostic groups Injected muscles varied depending on "distribution of spasticity"; no clear criteria for muscle and dose selection Nine of 17 subjects who received Dysport™ to the BB due to "associated flexor reaction" also had some improvement in various gait parameters
Bakheit et al (2001)[5]	n = 59; ≥3 mo post-stroke; MAS ≥2 in at least 2 of the elbow, wrist and finger flexors, and a score of 1+ in the remaining area	Injected placebo or Dysport™ 1000 u to BB, FCR, FCU, FDS, FDP	MAS	Improvement in summed MAS scores (elbow + wrist + finger flexors) at 4 wks post-injection in Dysport™ group compared to placebo, but at 16 wks (P = 0.004), individual muscle group MAS had significant differences only in wrist (P = 0.004) and finger flexors (P = 0.001) when compared to placebo MAS score change from baseline / Placebo / Dysport® 500 u* -4: 0 / 2 -3: 4 / 5 -2: 3 / 7 -1: 15 / 8 0: 10 / 5 *P = 0.004	No significant difference in ROM, Barthel Index, muscle pain, and goal-attainment scale

AS: Ashworth scale; BB: biceps brachii; DAS: Disability Assessment Scale; FAT: Frenchay Arm Test; FCR: flexor carpi radialis; FCU: flexor carpi ulnaris; FDS: flexor digitorum superficialis; FDP: flexor digitorum profundus; FIM: Functional Independence Measure; MAS: modified Ashworth Scale; PROM: passive range of motion; PT: physical therapy; RMAS: Rivermead Motor Assessment Scale; ROM: range of motion

reduction. Only one study investigated gait as a main outcome measure.[10]

In addition, a systematic comparison of the safety and efficacy of Botox® and Dysport® has not been performed.

Evidence of Efficacy of BTX type B

In the United States, BTX type B is marketed as Myobloc®, while in Europe and other countries it is sold under the trade name Neurobloc®. It was released more recently than Botox®; thus, published clinical research on its use for spastic hypertonia is limited. Only 1 open-label study has been published.[11] This study reported that Myobloc® (Solstice Neurosciences, Inc., Malvern, PA) significantly decreased upper limb spasticity, but the conclusion was made from studying a very small sample. Among 10 participants (1 TBI, 9 stroke) who received a total dose of 10,000 u to various muscles, including the biceps (3750 u), FCR (2500 u), FCU (2500 u), FDS (625 u), and FDP (625 u), AS scores improved significantly from baseline at 4, 8 and 12 weeks in all subjects. At week 4, AS scores improved significantly in the elbow ($P = 0.016$), wrist ($P = 0.004$) and finger flexors ($P = 0.02$). Dry mouth was the most commonly reported adverse effect. Two other small unpublished studies involving mixed diagnostic groups reported that Myobloc® (total dose range 4250 to 17,500 u) was effective in decreasing spastic hypertonia.[12,13] The relative superiority of Botox® or Myobloc® in terms of safety and efficacy has not been systematically investigated.

BTX Dosing Considerations and Clinical Decision-Making

For the purpose of this review, optimal dose will be defined in terms of efficacy, clinical effectiveness and safety. The optimal dose of BTX is the least amount needed to achieve a pre-determined outcome (e.g., decreased muscle tone, increased range of motion, improvement of function and hygiene) without causing an adverse effect (e.g., weakness). While it is acknowledged that the result of BTX therapy relies on various factors other than the actual amount of toxin injected, animal and clinical studies suggest that the dosage significantly influences outcome.[14,15]

Other factors may determine the outcome of BTX therapy and affect a clinician's decision regarding choice of dosage (Table 2). These include the following:

Table 2. Factors that Affect Dose Selection of BTX

Patient-related factors
Spastic hypertonia severity
Muscle and limb involvement
Spastic hypertonia duration
Age and body mass
Outcome of prior BTX treatment
Clinician-related factors
Experience, knowledge and expertise
Other factors
Cost
Availability of adjunctive therapy

BTX: Botulinum toxins

Patient-related Factors

Severity of spastic hypertonia. Higher BTX doses are required to treat more severe cases of spastic hypertonia.

Duration of deformity. Muscle shortening and soft tissue or arthrogenic contractures frequently accompany long-standing spastic hypertonia. Thus, other treatment options, such as serial casting or surgery, should be considered. In this situation, clinicians may even choose not to use BTX at all if contracture, rather than hypertonia, is the major cause of the deformity.

Muscle involvement. It may not be practical to use BTX as monotherapy when multiple muscles in a few limbs need to be treated. Treatment with more generalised effect, such as oral medications or intrathecal baclofen (ITB) therapy, should be considered. Another option is to use BTX in conjunction with phenol or alcohol neurolysis.

Age and body mass. In general, smaller doses are used in lower-than-average-sized individuals. In smaller children, doses are usually lower and expressed in terms of body weight.

Response to prior BTX therapy. Response to prior BTX doses should be an important factor in determining subsequent doses. When response to prior therapy is marginal, assuming that other factors have been ruled out (e.g., underlying contracture, inexact injection technique), the use of higher doses in subsequent treatment sessions should be considered. Conversely, if a certain dose results in an adverse effect, such as excessive weakness, lower doses of BTX should be used in the future.

Clinician-related Factors

First-hand experience. Treatment decision paradigms and techniques should be adopted by clinicians based on their experience with observed outcomes of prior BTX therapies.

Second-hand experience. Clinicians also apply knowledge obtained from sources other than their own experience from a colleague or scientific reports.

Other Factors

Cost. BTX therapy is not inexpensive. In mid-2006, the retail cost of 100 u of Botox® and 5,000 u of Myobloc® was about US$400 to US$500. Among the ways to contain costs is to combine the use of BTX with other medications, such as phenol or an oral spasmolytic agent. There is not yet

a comparative study on the cost-effectiveness of BTX and other spasmolytic therapies.

Concomitant therapies. Small, uncontrolled studies have reported that combining BTX with other therapeutic modalities may enhance the BTX's clinical effect. Some investigators have suggested that electrical stimulation of muscles injected with Botox®[10] or Dysport®[11] enhances the efficacy of BTX in improving muscle tone and gait, but these studies were limited by small sample sizes. Another report suggests that a "low dose" of Botox® (100 u) in conjunction with ankle taping results in improved ankle range of motion and foot positioning similar to that obtained with a "high dose" (190 to 320 u) but without subsequent taping.[16] The combined effect of BTX and physiotherapy and other therapeutic modalities in the stroke population has yet to be systematically investigated.

Dosing Frequency and Repeated Injections

The effect of repeated injections of BTX is rarely reported in the literature. A study of 28 stroke survivors who received Botox® every 3 to 5 months over a 2-year period to various upper limb muscles showed a sustained ability to respond to BTX.[17] Subjects received 25 to 75 u of Botox® to each muscle (total dose 50 to 300 u; mean dose per session 128 ± 32 u). Muscle tone, range of motion, and satisfaction and functional measures (e.g., putting on gloves, cleaning armpits) improved after each treatment. Over time, there was no change in doses used, but the intervals between treatment sessions grew longer, from a mean of 3.9 ± 1.2 months between the first 2 sessions to 6.4 ± 1.7 months between the fourth and fifth doses.

It is common clinical practice to inject BTX not more frequently than every 3 months, out of concern for antibody development.[7] This is based on findings in earlier studies on the use of BTX in cervical dystonia, where high initial doses, frequent injection, and "booster" injections were identified as factors contributing to the development of antibodies to BTX.[18] There is no published prospective study yet investigating the occurrence of antibodies specifically in spastic hypertonia.

Maximum doses of BTX

Since published studies have only reported the effect of BTX on a handful of muscles, mostly in the distal limb segments (arm, wrist, and finger flexors; ankle plantarflexors), dosing schedule has been based on clinical experience and expert consensus. A group of BTX experts have recommended that the maximum dose of Botox® is about to 400 to 600 u per session.[19] More experienced practitioners, however, have used doses as high as 900 u, but their experience regarding the safety and efficacy of higher doses of Botox® have yet to be systematically studied. A small open label study reported that the use of 600 units is efficacious in decreasing MAS scores and safe.[20] Similarly, maximum doses of Dysport® and BTX-B (Myobloc® in the US, Neurobloc® in Europe) for spastic hypertonia are not well established (Tables 3 and 4).

Why Haven't We Shown Functional Improvement?

In spite of the general consensus among clinicians and stroke survivors that BTX is effective in decreasing spasticity and in some cases enhancing residual function, studies have not demonstrated unequivocally that BTX is indeed effective in improving function. However, the assumption that BTX does not have a positive effect on function based on current studies alone goes against common clinical

Table 3. Recommended or Published Botox® Doses for Spastic Hypertonia due to Various Aetiologies

Upper limb muscles	**Dose (units)**	**Reference**
Subscapularis	50-100	19
Teres major	25-100	19
Latissimus dorsi	50-150	19
Pectoralis complex	75-150	19
Triceps	50-200	Author's experience
Biceps	50-200	1, 3, 19, 21, 22, 23
Brachialis	40-100	19
Brachioradialis		19
Pronator teres	25-75	19, 24
Pronator quadratus	10-50	19
Flexor carpi radialis	25-100	1, 2, 3, 19, 25, 26, 27
Flexor carpi ulnaris	20-70	1, 2, 3, 19, 25, 26, 27
Flexor digotorum superficialis	20-60	1, 2, 3, 19, 25, 26, 27
Flexor digitorum profundus	20-60	1, 2, 3, 19, 25, 26, 27
Flexor pollicis longus	10-30	19, 25, 27
Opponens pollicis	5-25	25
Adductor pollicis	5-25	19
Lumbricals	5-15 per lumbrical	19, 28
Lower limb muscles	**Dose (units)**	**Reference**
Quadriceps mechanism	50-200	19
Hamstrings	50-200	19
Hip adductor group	200-400	19, 29
Gastrocnemius	50-250	19, 30, 31, 32
Soleus	50-200	19, 30, 32
Tibialis posterior	50-150	19, 30, 32
Tibialis anterior	50-150	19
Extensor hallucis longus	50-100	33, 34
Flexor hallucis longus	25-75	19, 34
Flexor digitorum longus	25-100	19, 34
Flexor digitorum brevis	20-40	19

Table 4. Published Dyport® Doses for Spastic Hypertonia

Upper limb muscles	Dose (units)	Reference
Subscapularis	250	35
Biceps	100-400	9, 11, 36, 37
Brachialis	250	11
Brachioradialis	100	9
Flexor carpi radialis	150	9, 37
Flexor carpi ulnaris	100-150	9, 36, 38
Flexor digitorum superficialis	150-300	9, 36, 39
Flexor digitorum profundus	150-200	9, 36, 40
Lower limb muscles	**Dose (units)**	**Reference**
Hip adductor group	500-1000	38
Gastrocnemius	250-1000	39, 40
Soleus	200-500	39, 40
Tibialis posterior	200-500	39
Flexor digitorum longus	150-300	39

experience. The lack of scientific evidence is not an accurate reflection of BTX's effect on function, but rather may be due to limitations in study design and methods.

A fundamental problem is the widespread use of AS or MAS as primary outcome measures. While these scales are helpful in assessing tone, they do not characterise the speed-dependent nature of spasticity, which as defined by Lance[41] is a "velocity-dependent abnormality of tone, as one part of the upper motor neuron syndrome (UMNS)". Thus, the implicit assumption has been that decreasing spasticity will automatically translate into improving function. This oversimplifies function, which is multi-faceted and complex, as it is dependent not only on muscle tone, but also on other characteristics, such as muscle strength, coordination, endurance and muscle agonist-antagonist action. These other features are abnormal in UMNS, of which spasticity is but one component. In addition, the role of the sensory system on motor performance and the impact of cognition on functional abilities should not be overlooked.

In addition, valid functional outcome measures were seldom used in published studies. Most have utilised global scales, such as the FIM, which may not be sensitive to functional changes that are of clinical significance to an individual. The DAS was touted as a measure of disability, but for the most part is a measure of impairment (e.g., the domains of limb position and pain are not usually regarded as "function").

Poor patient selection may also have affected the study outcomes. If subjects have poor potential for motor and functional recovery, reduction of spastic hypertonia could not and should not be expected to result in improved function. Moreover, BTX injections may worsen residual function and induce transient weakness if too high a dose is used in muscles that do not have sufficient strength. Current dosages are primarily based on clinical experience, since studies have described doses for only a handful of muscles (most commonly the arm, wrist and finger flexors).

Interested readers are referred to Sheean[42] and Francis et al,[43] who have extensively reviewed and discussed why BTX therapy does not always translate into improved function.

Summary

BTX has been successfully shown to be an effective therapy for focal post-stroke spastic hypertonia, but the published literature has not convincingly demonstrated its impact on generalised spastic hypertonia and functional recovery. Future studies should pay particular attention to study design, including the selection of appropriate subjects and outcome measures. Also, the effect of BTX therapy on other muscle groups such as the proximal limb segments needs to be investigated, along with the interaction of BTX with other therapeutic exercises and modalities.

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