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FOCAL SPASTICITY THERAPY WITH BOTULINUM TOXIN: EFFECTS ON FUNCTION, ACTIVITIES OF DAILY LIVING AND PAIN IN 100 ADULT PATIENTS

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Objective: **Analysis of the effects of a comprehensive focal spasticity program in adult patients.**
Design: **Retrospective study of an out-patient cohort.**
Patients: **One hundred patients were enrolled in the study (54 men and 46 women, mean age 41 years (SD 14). Cerebral palsy and stroke were equally common (80% in total). The remaining patients had miscellaneous diagnoses, including traumatic brain injury.**
Methods: **On average 230 units (SD 101) of botulinum toxin A Botox® was given for 227 principal therapy targets chosen by the patient or the caregiver. One patient could have several targets for therapy. Administration of botulinum toxin was combined with 260 additional therapeutic interventions, most of which were forms of physical therapy. The effects were assessed after 6 weeks and compared with baseline functional abilities 1–2 weeks prior to therapy.**
Results: **Improvement was observed for 211 (93%) therapy targets, no change in 15 (7%), and impairment in 1, corresponding to an overall improvement in 90 patients (90%), 9 unchanged (9%) and worsening in 1. Spasticity assessment (Ashworth scale 0–4; 30 patients) showed a statistically significant improvement (median at baseline was 3 vs 2 after therapy, mean difference 1.2, $p < 0.001$).**
Conclusion: **Improvement was observed in $\geq$90% of patients and in their principal therapeutic targets in a cohort receiving their first focal spasticity treatment with botulinum toxin A and additional therapy. A strict strategy for patient selection and comprehensive management was followed.**

Key words: botulinum toxin, spasticity, adults, cerebral palsy, stroke, traumatic injury.

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INTRODUCTION

The 3 main factors affecting mobility in patients with damage to the central nervous system (CNS) are muscle over-activity (spasticity, rigidity, tremor, spastic co-contraction and spastic dystonia), motor weakness and soft tissue contractures (1). Muscle over-activity is usually unequally distributed in the muscle groups of an extremity, which causes imbalance between agonists and antagonists and contributes to functional impairment (1). Spasticity was defined in 1980 by Lance (2) as "a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the upper motor neurone syndrome (UMNS)". In patients with cerebral palsy (CP), stroke or traumatic brain injury (TBI), spasticity is an important mechanistic factor causing symptoms related to motor dysfunction, pain, contractures, etc. Spasticity therapy, whether pharmaceutical and/or surgical, usually in combination with physical and occupational therapy, has emerged as an important approach to alleviate such symptoms (3–8).

Pharmacological therapy may be systemic, using oral or intrathecal anti-spasticity medication, or local, with intramuscular, perineural injections and chemical neurolysis. Antispasmodic oral drugs non-selectively depress CNS responses and may cause side-effects such as generalized muscle weakness, fatigue, sedation and cognitive impairment. In severe and/or more generalized spasticity, oral agents and intrathecal baclofen may, however, provide relief (1, 9).

Chemodenervation by local injections of botulinum toxin type A (BTX-A) is a relatively new pharmacotherapeutic option approved in 1989 in the USA, and in 1992 in Sweden. Botulinum toxin reduces spasticity in selected muscles by blocking acetylcholine release at the neuromuscular junction. The effect lasts about 3–4 months. The temporary decrease in muscle tone permits physical and occupational therapy interventions, such as muscle strengthening and facilitation, increasing range of motion, retraining of ambulation and gait, improving function in activities of daily living (ADL) and the fit and tolerance of orthoses (4, 10, 11).

Surgical interventions, such as dorsal rhizotomies, nerve root resections, myotomies, and tenotomies, may prevent spasticity, and prevent or correct contractures and deformities (12, 13).

An outpatient program of focal spasticity therapy in adult patients was initiated in our department in 1999. Since experience was limited, especially in adult patients with CP, but also with TBI, we developed and adhered to strict selection and exclusion criteria from the beginning, allowing subsequent systematic evaluation.

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Studies describing effects of comprehensive management with additional therapeutic interventions are rare. The aim of the present retrospective analysis was therefore to assess the therapeutic targets and effects on functions, ADL and pain, after focal spasticity therapy including botulinum toxin and physiotherapy, in a consecutive series of our first 100 patients with CP, stroke and TBI.

MATERIAL AND METHODS

Patients

Over a period of 4 years (1999–2003), 54 men and 46 women, mean age 41 years (SD 14), age range 18–73 years) of 124 consecutive first referrals were included in this study. All the patients fulfilled the criteria for focal spasticity therapy (see selection procedure), and the quality requirements for this study. The latter were a 3-month follow-up period and adequate clinical records. Grouped by diagnostic category, 41 had CP (16 spastic diploid, 15 quadriplegia, 6 hemiplegia and 4 spastic dystonia), 39 stroke, 15 TBI and 5 miscellaneous diagnoses (1 Rett syndrome, 2 anoxic brain injury, 1 tumour and 1 paraplegia of unknown aetiology). Stroke and CP were equally common and together constituted 80% of the diagnoses. The patients with stroke were older (mean age 50 years (SD 11)) than those with CP (mean age 33 years (SD 12)). Seventy percent of the patients were internal department referrals and the rest external. The time interval between the index event and inclusion in the study was for stroke 5 months to 5 years (2 patients <6 months, 3 patients 6–12 months, and 34 patients >12 months), for TBI 3–9 years, and for the "miscellaneous group" 2–40 years.

Fifteen referrals were judged unsuitable for focal spasticity therapy, 7 received injections but did not pursue the treatment plan (additional therapy and splinting), 1 was referred for treatment with baclofen and 1 had incomplete documentation.

Selection procedure and baseline assessment

At the first visit the patient was assessed by a multidisciplinary clinical team, which decided whether to offer focal spasticity therapy by injecting botulinum toxin (Table I). The team comprised a physician, a nurse, a physical therapist and, occasionally, an occupational therapist and an orthopaedic technician. All the patients or their caregivers gave informed consent to the therapy program.

The selection criteria for focal therapy were:

- at least one principal therapeutic target chosen by the patient or caregiver;
- identification of a well-defined clinical problem for which spasticity was judged to be a crucial component, and remediable provocative factors could be excluded
- absence of contractures
- access to additional therapy such as physical and occupational training, splinting, orthoses, and assisted home training

The principal therapeutic targets were in general (Table II).

- maintenance or enhancement of self-administrated functions: gait, standing, transfers, wheelchair management and active ADL
- facilitation of physical/occupational/speech therapy
- pain relief
- facilitation of caregivers' tasks in ADL (passive-ADL)
- improvement of fit and tolerance of orthoses
- pressure sore reduction
- prevention of involuntary movements
- cosmetic targets

Following the decision on focal spasticity therapy, target muscles for BTX-A injections were selected on the basis of clinical examination and patients' choice of target. Plans were also made for the additional necessary interventions (training, splinting, etc.).

In addition, clinical outcome measures were selected, and a baseline assessment was made by the treating physical therapist, or if the patient did not yet have a therapist contact, by the physical therapist at the spasticity clinic. In line with the practice in neurological rehabilitation (14, 15) a verbal scale for patients' and/or caregivers' self-reports of therapy effect was used in all cases. The verbal scale was comparative in the simple form of: worse – the same – better. Individual outcome measures were selected as deemed relevant in relation to the principal therapeutic targets (Table III). In 30 patients, muscle tone was assessed by the degree of resistance to passive movement of the target muscle group according to the Ashworth Scale (0-4) (16). When standardizing testing protocols, account was taken as far as possible of optimal subject testing position, control for velocity of passive stretching, and range of movement.

All these steps were taken at the first visit.

Therapeutic procedure

At the second visit, intramuscular injections (Botox® Purified Neurotoxin Complex, Allergan, Inc., Irvine, CA, USA) were given in muscles exhibiting muscle over-activity. Dosing was based on the 1997 guidelines for "Dosing and administration, and a treatment algorithm for use of

Table I. *Critical components of the assessment at the first patient visit according to our scheme*

Selection by patient or caregiver of principal therapeutic target
Functional analysis
Biomechanical analysis
Identification of spastic muscles, degree of spasticity and potential "triggers"
Assessment of activity of antagonistic muscles (when considering patient function)
Identification of contractures
Selection of outcome measures
Planning of additional therapy and follow-up
Evaluation of patient motivation (anticipated treatment compliance)

Table II. *Indication for and results of treatment. Results of treatment. Number of patients improved in relation to total number of patients with each indication*

Indications for treatment	Improved *n* (%)	95% CI
Improvement of mobility (ambulation, gait pattern)	37/43 (86)†	72–95
Facilitation of physical and/or occupational therapy	35/35 (100)	90–100
Pain reduction	30/32 (94)†	79–99
Improvement of active-ADL	24/28 (86)‡	67–96
Facilitation of passive-ADL	20/22 (91)†	71–99
Facilitation of orthosis wear	16/16 (100)	79–100
Improved sitting	11/11 (100)	71–100
Improved standing	9/10 (90)†	55–100
Pressure sore reduction	8/8 (100)	63–100
Improved transfer	6/7 (86)†	42–100
Improved wheelchair management and mobility	5/7 (71)†	29–96
Prevention of involuntary movements	4/4 (100)	40–100
Cosmetic issues	2/2 (100)	16–100
Other*	2/2 (100)	16–100

*Mouth hygiene, facilitation of speech therapy, prevention of luxation.
†Unchanged result for the remaining patients.
‡Three were unchanged and 1 patient got worse.
ADL = activities of daily living.

Table III. *Individually selected standardized outcome measures in relation to indication for therapy. Additionally, in all subjects a verbal scale (worse – the same – better) was used when gauging individual responses to treatment*

Indication	Outcome measures
Impairment measures	
Spasticity	Ashworth scale, spasm frequency count
Joint ROM	Goniometry, length-/distance measurement
Pain	Visual analogue scale
Power	Jamar-dynamometer, Medical Research Council scale
Activity	
Gait	Video: gait analysis, walking speed, stride length
Wheelchair mobility	Video: timed course/-transfers
Functional abilities	Video/photo: analysis/timed activities of daily living, Nine-hole peg test, Canadian occupational measurement
Participation	
	Short form-36, Canadian occupational measurement

ROM = range of movement.

BTX-A for adult-onset spasticity'' (17, updated version 18). The injections were guided by electromyographic recording technique to define the presence of abnormal muscle activity (19).

The mean dose of BTX-A in one set of injections was 230 U (SD 101) (range 25–500 U). In patients with CP it was 245 U, in patients with stroke 210 U, in patients with TBI 225 U, and in those with miscellaneous disorders 200 U. A total of 351 muscles (1–5 per patient) were injected (130, 142, 62, and 17 in the CP, stroke, TBI and the miscellaneous group, respectively). Upper and lower extremities were equally frequent targets ($n = 58$). In 16 patients (9 stroke, 4 CP and 3 TBI) both upper and lower extremities were treated (Fig. 1).

In addition to the injections, further therapeutic interventions were provided in all 100 patients. Physical therapy treatment was given in 70 cases (CP 21, stroke 31, TBI 13 and miscellaneous 5), assisted home training in 43 (CP 21, stroke 9, TBI 10 and miscellaneous 3), an individualized patient home training program in 40 (CP 14, stroke 20, TBI 4 and miscellaneous 2), occupational therapy treatment in 18 (CP 0, stroke 12, TBI 5 and miscellaneous 1), and speech therapy in 1 patient with TBI; altogether 172 training interventions. Lower- and upper-extremity orthoses were made in 40 and 28 cases, respectively, and orthopaedic shoes and footwear corrections in 20. Thus 260 interventions were provided in addition to the injection sets.

Follow-up

The first follow-up visit was scheduled for 6 weeks after the injections, at which time patient status, treatment effects, functional gains, patient's satisfaction and compliance as well as any adverse event were evaluated by the referring therapist or the patient's physician (see baseline assessment). At the follow-up visit it was also decided whether to plan for a repeated set of injections, based on the response to the first set. In cases of re-injection another follow-up visit was scheduled 12 weeks after the injection, according to the recommended injection intervals of no less than 3 months (17, 18).

Statistical analysis

For descriptive purposes mean and standard deviation or median and range were used. Exact 95% confidence intervals (95% CI) were applied as appropriate, and obtained from the *Geigy scientific tables* (20). Scores on the Ashworth Scale at baseline and after intervention were analysed with the Wilcoxon matched pairs signed-rank test.

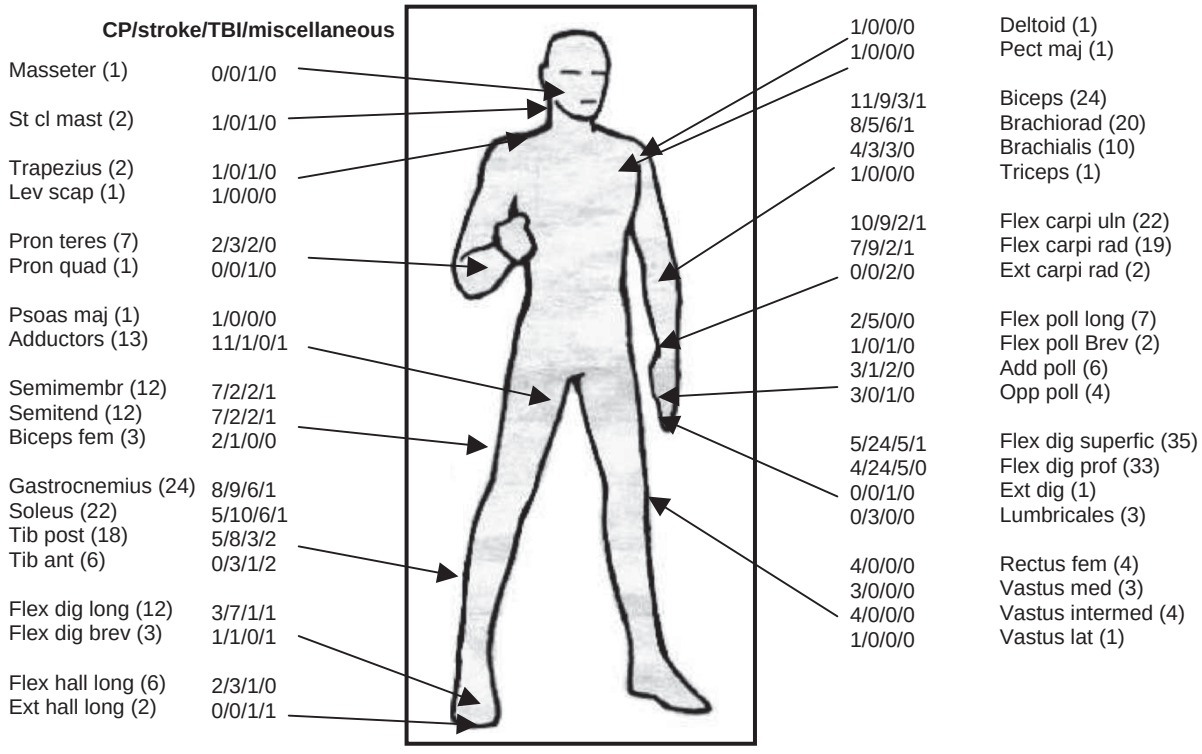

Fig. 1. Anatomical distribution of target muscles for injection of botulinum toxin A in relation to diagnosis presented as cerebral palsy, stroke, traumatic brain injury, or miscellaneous.

Statistica version 6.1 (StatSoft, Inc, Tulsa, OK, USA) was used for the analysis

RESULTS

Principal therapeutic target

There were 227 indications for treatment, i.e. on average ~2.3 per patient. In 50% of the patients there was one indication, while the maximum was 5 in any single patient. The patients' or caregivers' chosen principal targets are specified in Table II. The 3 main targets ($\geq$1 per case) for therapy in patients with stroke (n=39) were gait improvement in 19 patients, and therapy facilitation and active-ADL in 18 and 14 patients, respectively. In patients with CP (n=41) the target was gait improvement in 15, and pain reduction and facilitation of passive-ADL in 15 and 11, respectively. In patients with TBI (n=15) the main targets were gait improvement in 7, therapy facilitation in 8, pain reduction and help with wearing orthoses in 5 each. In the miscellaneous group (n=5) improvement of gait in 2 patients, pain reduction in 2, and facilitation of active and passive-ADL were the targets in 1 patient each.

Treatment effects

In relation to the 227 principal therapy targets, improvement ("better") was reported in 211 (93%), no change ("the same") in 15 (7%), and impairment ("worse") in 1 patient. This corresponds to an overall improvement in 90 patients (90%; 95% CI 82–95), 9 unchanged (9%; 95% CI 4–16), and worsening in 1 (1%; 95% CI 0–5). The efficacy was the same for upper and lower extremities, 52 of 58 for each (90%; 95% CI 79–96). In 5 patients with CP there was no change in gait (3), transfer (1), wheelchair management (1), active-ADL (1), or pain (1). In 2 patients with stroke no changes were observed in gait (2), active-ADL (1), pain (1), or passive-ADL (1), and in 2 patients with TBI there were no changes in active-ADL (1), passive-ADL (1), or wheelchair management (1). One patient with stroke reported worsening in active-ADL.

In the 30 patients where assessment of spasticity according to the Ashworth Scale was documented, the median score before intervention was 3 (mean 3.2; range 1–4). After intervention the median was 2 (mean 2.0; range 0–3), with an average improvement of 1.2 (p <0.001).

The subgroups were too small to allow meaningful analysis of the individualized outcome measures listed in Table III.

However, in addition to the improvements related to the patients' chosen targets and treatment goals, there were in 31 cases reports of other and unexpected improvements ($\geq$1 per case), which might be related to the therapy ("positive side-effects"), such as in passive-ADL in 11 patients, speech, balance, increased social participation in 4 patients each, decrease in clonic cramps in 5 patients, improvements in sleep, stamina, cosmetics and pain relief, and reduction in seizures, in 1 patient each.

Re-treatment was given in 62 patients (CP 26, stroke 24, TBI 8 and miscellaneous 4) 3–6 months after the first set to prolong efficacy and to facilitate further therapy.

Safety

Nine patients reported transient adverse symptoms ($\geq$1 per case): muscular weakness in 6 patients, tendonitis in 3 patients, and in 1 patient each: neuralgia, constipation and seizure on the day of injection in a patient with frequent episodes.

Inter-current diseases/diagnoses not considered to be related to the present therapy occurred during the 3-month follow-up period in 10 patients ($\geq$1 per case): pneumonia in 4 patients, seizure in 3 patients, low back-pain in 2 patients, and diabetes, pulmonary embolism, spinal stenosis, upper respiratory infection, and burn injury, in 1 patient each.

There was no report of major change in medication during the 12-week period, but 4 patients received penicillin, 1 warfarin, 1 was started on baclofen which was withdrawn, 1 received carbamazepine, and another risperidone.

DISCUSSION

In this consecutive series, 100 carefully selected adult patients with disabilities judged to be caused by spasticity were treated at an outpatient clinic. Improvements were observed in 90 patients or 211 of the 227 therapy targets, following the first set of injections of BTX-A for focal spasticity treatment. Importantly, these results were obtained by combining the injections with on average 2.6 additional interventions per patient, the majority related to physical therapy, individualized training and orthoses.

To our knowledge this kind of descriptive, retrospective study, following consecutive adult patients' first set of injections and with a comprehensive management approach has not been reported previously in English, even though focal spasticity therapy in adult patients was reported in 1989 (21). Studies on focal spasticity therapy in adult patients with CP and TBI are also rare.

This is a retrospective analysis with the well-recognized limitations of such a study. When setting up our program in 1999, the Royal College of Physicians' *Guidelines for the use of botulinum toxin (BTX) in the management of spasticity in adults* had not been published (3). At the time, the *Muscle & nerve supplement 6/1997* could be followed (22). However, our clinical experience clearly showed that a firm strategy for focal spasticity therapy was needed. Our model, as outlined in Table I, was tentative and therefore a systematic evaluation was planned early on. Furthermore, the patient selection criteria and the principles for choosing targets were predefined. The follow-up visits were also planned and conducted in a consistent manner. Throughout the period covered in this retrospective analysis there were no major changes in the management strategy, which also turned out to be similar to what subsequent guidelines suggest.

In our patients with UMNS, comprehensive management was complex due to a wide range of clinical problems in addition to those related to the principal therapeutic goal, such as impaired communication, cognition and/or visual-spatial skills. The number of individualized outcome measures reflects these difficulties, as does the heterogeneity of the patient problems – as in clinical reality. In the clinic we used the impairment scales and measures of activity and participation or quality of life as listed in Table III. However, we consistently used the verbal scale as outcome measure in all patients. Since this instrument is short and simple, patients or caregivers could easily express their judgement. This approach is in line with practice in neurological rehabilitation, as previously suggested (14, 15) and subsequently included in the 2002 *Guidelines* (3). The verbal scale is relatively reliable since there are few possibilities, but it therefore also has a limited sensitivity (3). Its self-reports correlated well with our clinical assessments as well as with what the Ashworth scale showed in 30 patients. The observed average improvement from baseline of 1.2 tallies with the significant results of a previous report (23).

In a recent large placebo-controlled study, in which patients' choices of the principal target for their treatment was evaluated with standardized outcome measurements, 40 of 64 patients improved (62%; 95% CI 50–74) (24). There was, however, no report of adjunctive therapy, as subsequently commented upon (25). We report improvement in 90 patients (90%; 95% CI 82–95). Adjunctive therapy (on average 2.6 interventions per patient) probably played an important role in achieving the treatment benefits reported, in line with previous observations (4, 26, 27) and general notions (3, 17). The comprehensive management and multidisciplinary work necessary in neurological rehabilitation makes it difficult, however, to distinguish the effects of separate therapeutic components in relation to the outcome during follow-up.

The clinical consequences of spasticity vary widely between patients. In rehabilitation, the main clinical objective of spasticity treatment is generally improvement of patient functions, such as gait, standing ability, transfers, wheelchair management and ADL. Improvement in active performance is sometimes difficult to demonstrate (9, 18), but has previously been reported with regard to ability to walk and stand in patients with spastic equinovarus or equinovalgus foot/ankle deformities and in patients with knee-flexor spasticity (8, 28). In our study 71–90% of the patients reported improvement in functional goals after therapy (Table II).

However, functional gains are not always the first priority for the individual patient. Instead improvement of quality of life related to pain relief, help with wearing orthoses, cosmetic issues, pressure sore reduction, and prevention of involuntary movements, might have the highest priority (27).

Although the effectiveness of BTX-A in spasticity therapy has been reported in studies with different design, including at least 8 large randomized controlled trials on spasticity reduction after stroke (7, 8, 24, 28, 29–32), there are still doubts about the efficacy of this treatment (25, 33). One reason is the improvement observed also in the placebo group (24). This presumed "placebo effect" might at least partly be related to other therapeutic measures than BTX-A injections.

In our study spasticity-related local pain was the indication for injections in 32 patients. All except 2 reported pain relief at follow-up, in line with a previous large study in which a significant reduction of pain was reported in 90% of patients with UMNS (34). In yet another study pain reduction was seen in 28 of 31 patients (35). Adverse effects are usually fairly uncommon (17). In this study transient adverse effects were seen in 9 patients, of whom 6 reported mild reversible muscle weakness, also reported previously (35). This may be eliminated by modifying the dose (17). Tendonitis symptoms (muscle tendon painful in activity, stretch and on palpation) were reported by 3 patients, were probably due to a changed pattern of movement, and were reversed within 1–2 weeks.

To optimize outcome, it is crucial for a focal spasticity service to establish a management model that includes all critical components of a comprehensive therapeutic procedure. A multidisciplinary team was essential for managing the complex spasticity-related problems and developing an overall management plan together with the patient or caregiver. When setting goals, careful assessment and clinical reasoning were of the essence. The assessment was based upon patients' selection of their principal therapeutic target. However, further studies are needed to find appropriate and sensitive measures of motor performance and spasticity that can be applied to a majority of patients.

In conclusion, improvement was observed in $\geq$90% of patients and principal therapeutic targets in a cohort receiving their first focal spasticity treatment with botulinum toxin A and additional therapy. A strict strategy for patient selection and comprehensive management was followed.

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