

Functional influence of botulinum neurotoxin type A treatment (Xeomin®) of multifocal upper and lower limb spasticity on chronic hemiparetic gait

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Abstract

This report describes the modification of hemiplegic shoulder pain and walking velocity through injections of Xeomin®, a new botulinum neurotoxin type A formulation, in a 67-year-old woman with chronic residual left hemiparesis and hemiparetic gait attributable to stroke. Clinical evaluation included upper and lower limb spasticity, upper and lower limb pain, trunk control, upper and lower limb motricity index, visual gait analysis, and gait velocity. Assessments were performed before, 1 week after, and 1 month after treatment. Improvement was observed in all clinical parameters assessed. Amelioration of spasticity of the upper and lower limbs and shoulder pain was observed after 1 month. Trunk postural attitude and paraxial muscle recruitment recovered. No adverse events were observed and the patient shows significant improvement of functional impairment derived from chronic spasticity after treatment with Xeomin®. We also provide a simple and useful protocol for clinical evaluation of the treatment.

Introduction

Botulinum toxin type A (hereafter referred to as botulinum toxin) is a valuable treatment option for functional problems related to spasticity following brain injury. In Europe, a consensus has been reached to define best practices for the use of botulinum toxin in the management of spasticity following adult acute injury.¹ Two formulations of botulinum toxin have been used in the treatment of spasticity and hemiparetic gait:²⁻⁶ Botox® (Allergan Inc., Irvine, CA, USA) and Dysport® (Ipsen Biopharm Ltd, Wrexham, UK). Botulinum toxin in these preparations is obtained from *Clostridium botulinum* as part of a high molecular weight complex with hemagglutinins and

other non-toxic proteins of clostridial origin that may contribute to the development of neutralizing antibodies and secondary non-responsiveness to treatment.^{7,8} A botulinum neurotoxin preparation, free from complexing proteins, Xeomin® (Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany), has become available in recent years,⁹⁻¹³ and has been associated with reduced immunogenicity in animal models.¹⁴ In Italy, Xeomin® is currently indicated for the treatment in adults of blepharospasm, cervical dystonia of a predominantly rotational form (spasmodic torticollis), and post-stroke spasticity of the upper limb presenting with flexed wrist and clenched fist. Therefore, in clinical practice, Xeomin® may be less likely to generate neutralizing antibodies and non-responsiveness to treatment.¹⁵

Phase I studies have demonstrated the paralytic effect of Xeomin® 4 IU injected into the *extensor digitorum brevis* muscle of both feet in healthy volunteers;¹⁶ similar results were observed when higher Xeomin® doses (up to 32 IU) were used.¹⁷ Clinical studies have demonstrated the efficacy of Xeomin® in the treatment of cervical dystonia,¹⁸ blepharospasm,¹⁹ and upper limb spasticity.¹¹⁻¹³ However, no further clinical information exists on the tolerability or the efficacy of Xeomin® treatment on functional problems (e.g. spastic gait, hemiplegic shoulder pain in upper limb hypertonia, rheologic muscle modifications) following acquired brain injury in adults. This report describes the assessment of hemiplegic shoulder pain, functional limb muscle performance, and walking velocity in a patient with multifocal upper and lower limb spasticity after treatment with Xeomin®.

Case Report

A 67-year-old woman was diagnosed with a complex regional pain syndrome, primarily in the upper left limb, that was attributable to hemorrhagic right hemisphere stroke. The patient showed spastic upper limb monoplegia, spastic equinovarus foot, trunk push syndrome and left lateral shift of the center of mass with global postural instability induced by the asymmetric postural attitude. She had difficulty in maintaining a vertical position and her ability to walk, either assisted or with a walking aid, was impaired. At initial examination, she had been undergoing physiotherapy for at least 2 months post-stroke, which consisted of postural control exercises, gait training, and passive and active upper and lower limb kinesiotherapy. She was receiving anti-spastic therapy (baclofen and pregabalin).

Initial clinical evaluation consisted of an assessment of: upper and lower left limb spasticity [modified Ashworth scale (MAS)]; grad-

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ing of pain [visual analog scale (VAS)]; trunk control capacity in specific motor performances [trunk control test (TCT)]; upper and lower limb motor function [motricity index (MI)]; visual gait analysis (VGA) performed while walking barefoot over a distance of 12 meters, grading initial foot contact during the stance phase (normal heel strike=0; flat foot=1; toe then heel=2; mild toe-walking=3; marked toe-walking=4; change of one grade was considered clinically significant); gait velocity, determined by dividing the distance of a walkway (10 meters) by the time the patient needed to cross it at maximum speed, with supervisor and without using gait help. Five days after the initial evaluation, the patient underwent an injection session with Xeomin®. Xeomin® was reconstituted with saline to a final concentration of 50 IU/mL. The total dose administered was 400 IU, in accordance with published guidelines for the management of spasticity.²⁰ The muscles to be injected were identified using surface anatomy and the doses injected in the different muscles are given in Table 1. Injections were administered under sterile

Table 1. Doses of Xeomin® administered to individual muscles.

Clinical pattern Muscle injected	IU of Xeomin® administered Per muscle	Total
<i>Intrarotated shoulder</i> Left pectoralis complex	50	50
<i>Flexed elbow</i> Left biceps	150	150
<i>Clenched fist</i> Left flexor digitorum profundus Left lumbricalis	60 40	100
<i>Equinovarus foot</i> Left tibialis posterior Left soleus	60 40	100

conditions using standardized techniques. Physiotherapy, as described previously, was performed during and after the injection session. In addition, electrical surface stimulation of the injected muscles was performed two times per day for 3 days, and daily application of a dynamic palmar and elbow extension orthosis for 4 days.

One week and 1 month after the injection session, the patient was examined again by the same physician. Three measurements of each clinical parameter or gait velocity were performed at each examination and the mean value was calculated to quantify the effect of treatment with Xeomin®. After a one-way analysis of variance (ANOVA) of our results, only a descriptive review of the therapy outcome can be given.

Clinical examination performed before and after Xeomin® administration demonstrated its efficacy at reducing spasticity in the upper and lower limbs, decreasing the MAS 1.3- and 1.7-fold, respectively, at 1 month after treatment (Figure 1A). In the upper limb, a marked amelioration in pain intensity was observed, reflected by a 3-fold reduction in VAS after 1 month (Figure 1B), an improvement of comparatively greater magnitude than that observed in spasticity. Trunk postural attitude and paraxial muscle recruitment were enhanced after Xeomin® treatment as seen by an increased TCT (Figure 1C). Recovery of motor function of the left upper limb was reflected by an increased MI after 1 month (Figure 1D), although motor function of the lower limb was not affected. Better left foot contact during the gait cycle also followed administration of Xeomin®, with significant VGA score reduction after 1 month (Figure 1E). Walking speed increased after treatment (Figure 1F). None of the adverse events most frequently associated with botulinum toxin treatment (headache, dysphagia, and weakness) were observed after the treatment. Flu-like symptoms, which have been reported for other botulinum preparations, were also not reported with the use of Xeomin®.

Discussion

The main finding of this evaluation was that a task-specific treatment with Xeomin® of chronic upper and lower limb spasticity decreased hemiplegic shoulder pain and modified hemiparetic gait, without adverse events, in a patient with functional disorders attributable to stroke.

Xeomin® is a botulinum neurotoxin preparation free from complexing proteins. The

absence of potentially immunogenic complexing proteins can be a distinct therapeutic advantage, especially for those patients who require long-term treatment with high doses of botulinum toxin, such as the patient presented here.²¹ Experience with Xeomin® has accumulated in recent years, with data now available across multiple indications.¹⁰ Kanovsky *et al.*¹¹ first demonstrated the task-specific efficacy of Xeomin® in reducing muscle tone and disability in patients with post-stroke upper limb spasticity, based on Ashworth Scale score assessment. Subsequently, in an open-label extension study, repeated injections were shown to provide sustained efficacy in this population over a duration of up to 89 weeks.¹² Meanwhile, case studies are providing insight into applications in the treatment of lower limb spasticity. For example, Xeomin® was shown to improve muscle tone in a patient with spastic equinovarus following acquired brain injury.²² However, the influence of Xeomin® treatment of upper limb spasticity on hemiparetic gait has not been documented to date.

This interventional evaluation is, to our knowledge, the first observation confirming the efficacy of Xeomin® on hemiplegic shoulder pain and chronic hemiparetic gait in multifocal upper and lower limb spasticity. While

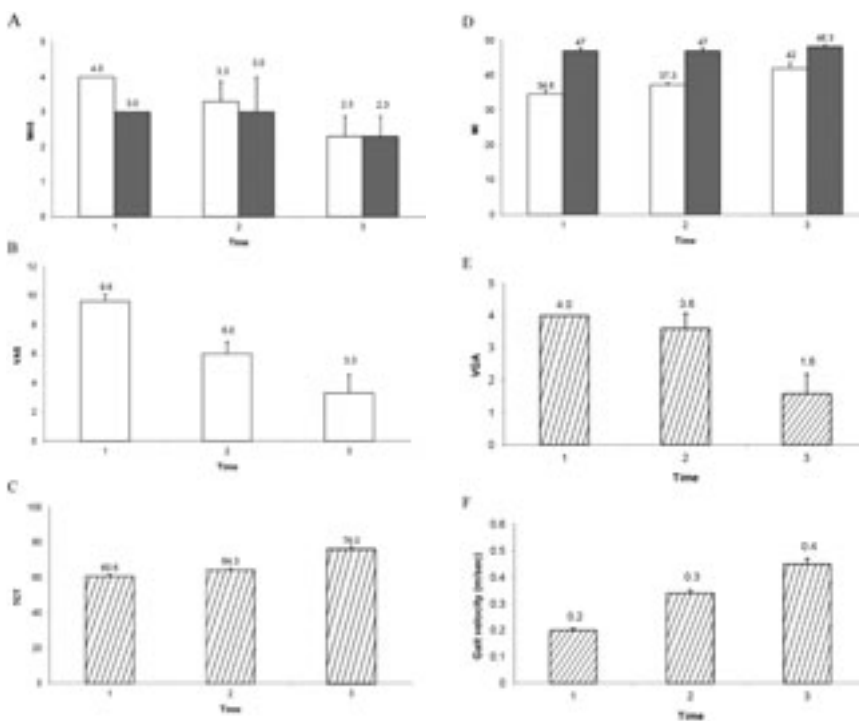


Figure 1. Clinical and functional measurements before, 1 week, and 1 month after Xeomin® administration. A) Spasticity (Modified Ashworth Scale [MAS]); B) Pain (visual analog scale [VAS]); C) Trunk control capacity (TCT); D) Motricity index (MI); E) Visual gait analysis scores (VGA); F) Gait velocity. Numbers given are mean values, with error bars representing standard deviation of three measurements. Open and closed bars represent upper and lower limbs, respectively; hatched bars are used for tests not performed in limbs.

this represents a single case, it is concordant with previous studies of Botox®: in one study, the treatment of elbow flexor spasticity (total dose: 120-200 U) was shown to improve walking velocity in patients with hemiparesis following stroke or traumatic brain injury,² while in another study, the treatment of several spastic muscle groups (total dose: 300-500 IU) was shown to increase knee flexion and improve locomotion ability in patients with hemiparesis following stroke.³ In the second of these studies, the total dose of Botox® was in a similar range (300-500 IU) to the total dose of Xeomin® used in the case presented here (400 IU). We propose that further studies of botulinum toxin for the improvement of functional disorders associated with multifocal post-stroke spasticity are warranted to confirm these observations in a larger patient population.

We also show the usefulness of simple scores to quantify clinical changes and functional influence of treatment, in line with attempts reported in other studies.^{2,3,6} By reducing the hypertonus of proximal and distal spastic muscles of the upper limb, the patient's own grading of pain significantly decreased, arm voluntary function during normal daily activities improved, and trunk postural attitude and paraxial muscle recruitment increased, enabling sitting and maintenance of a vertical position. We believe that a task-specific reduction of upper limb pain and of plantar flexor and invertor muscle tone resulting from Xeomin® treatment could modify global postural attitude of the patient, facilitating comprehensive physiotherapy and the recovery and amelioration of gait disturbance.

Conclusions

This case study demonstrated that a single injection session with 400 IU of Xeomin® to upper and lower limb muscles can contribute to improving gait disturbance, and reducing disability and caregiver burden. Further studies are needed to extend these encouraging results to a larger population affected by functional disorders related to multifocal limb spasticity secondary to stroke.

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