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Original Article

Gait improvement by low-dose botulinum toxin A injection treatment of the lower limbs in subacute stroke patients

Wu Tao[1)], Dong Yan[2)*], Jian-Hua Li[1)], Zhao-Hong Shi[3)]

[1)] *Department of Rehabilitation, Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University, China*
[2)] *Department of Rehabilitation Medicine, Hangzhou Hospital of Zhejiang CAPF: Jiang Nan Road, No. 86, Hangzhou 310016, China*
[3)] *Department of Rehabilitation, First People's Hospital of Wen-ling, China*

Abstract. [Purpose] Lower-limb spasticity after stroke may be associated with worse functional outcome. Our study aim was to establish whether a low-dose botulinum toxin A (BTX-A) injection in subacute stroke patients can improve spasticity, gait, and daily living abilities. [Subjects] Twenty-three subacute stroke patients were randomly allocated to BTX-A treatment group (11 patients) and control group (12 patients). [Methods] In the BTX-A treatment group patients, 200 units BTX-A was injected into the triceps surae (150 iu) and posterior tibial (50 iu) by electrical stimulation-guided. The patients in the control group received the same volume of placebo solution into the same injection locations. Gait analysis (step length, cadence, speed), the 6-min walking test, Fugl-Meyer Assessment (FMA) of the lower limbs, modified Ashworth scale assess (MAS) assessment of the lower limbs, surface electromyography (sEMG), and modified Barthel index (MBI) assessment were performed before and at 4,8 weeks after treatment. [Results] We found that the FMA of the low limbs and MBI were significantly improved in both groups. The gait analysis, FMA, and MBI results in the BTX-A treatment group were better than those in the control group. MAS and surface electromyography (sEMG) showed better improvement of spasticity in the treatment group. [Conclusion] Early low-dose botulinum toxin A (BTX-A) injection in subacute stroke patients into the lower-limb may improve gait, spasticity, and daily living abilities.
Key words: Botulinum toxin A, Stroke, Spasticity

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INTRODUCTION

In patients with lower-limb spasticity after stroke, spastic equinus foot represents a prolonged abnormal lower-limb posture and affects gait, standing, and transfer[1)]. Poststroke lower-extremity spasticity may cause severe functional limitations and pain. Spasticity is a phenomenon defined as disordered sensorymotor control, resulting from an upper motor neuron lesion and presenting as intermittent or sustained involuntary activation of muscles. Stroke often affects sensorimotor networks and descending tracts, as reflected by the negative and positive signs of upper motor neurone (UMN) syndrome[4)]. Spasticity causes motor incoordination, which is more associated with gait speed than positive features[2)]. Spasticity may interfere with motor function and is a common reason for clinical interventions such as physiotherapy, use of orthoses, or other technical devices or drugs[3)]. Botulinum toxin type A (BTX-A) is a potent neurotoxin produced by the bacterium clostridium botulinum. BTX-A blocks acetylcholine release at neuromuscular junctions, which accounts for its therapeutic action in relieving dystonia, spasticity, and related disorders. Intramuscular injections of botulinum toxin are used to target one or more of the positive signs of UMN syndrome[5)].

The reported prevalence of spasticity according to the Modified Ashworth Scale (MAS) at 3 months or later after first-ever stroke in studies of unselected, consecutive patients after stroke is around 20% or higher[6, 7)]. Early identification of potentially disabling spasticity is important to enable preventive intervention. Patients with initially severe limb paresis are at higher risk for developing spasticity[7–11)].

Unfortunately, intramuscular injections of botulinum are often carried out when the patients have obvious spasticity[12)]. It is normally given once the clinical signs of elevated muscle tone have become established; therefore, it is usually given at least three months after stroke[13, 14)]. This will impede rehabilitation of the patients. Accordingly, the present pilot study asked whether early lower-limb injection of low-dose botulinum toxin A (BTX-A) in severely affected patients within 4–6 weeks after stroke could help to prevent

*Corresponding author. Dong Yan (E-mail: 402101198@qq.com)

disabling muscle stiffness and walking dysfunction 8 weeks later.

SUBJECTS AND METHODS

This was a single-center phase II randomized double-blind placebo-controlled pilot study. Patients were recruited from the stroke/neurology units or rehabilitation department of Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University. All patients gave informed consent. The study had ethics permission from the ethics committees of the College of Medicine of Zhejiang University.

Adults with hemiplegic stroke and severe or moderately severe spasticity following stroke were recruited. The inclusion criteria for the patients were as follows:

1. They were over the age of 18 and less than 80 years and had had a stroke within 6 weeks.
2. They had slight spasticity of the triceps surae as defined by a score of 1–1+ on the MAS or ankle clonus (+).
3. They had sufficient cognitive and communication ability as defined by an MMSE (mini-mental state examination) sore >25.
4. They could not dorsiflex the ankle and their LEMI (Lower Extremity Motor Index)< 10[9].
5. They were not receiving concurrent aminoglycoside antibiotics or oral anti-spasticity medication.

Twenty-three eligible patients focused on early stroke rehabilitation were recruited (Table 1). These patients were randomly assigned with the help of a computer-generated list to either the experimental or control group.

In group A patients (experimental group, n=11), an experienced physician injected 200 units BTX-A (Allergan, 1 ml dilution per vial) by electrical stimulation-guided (Dantec CLAVIS^{TM}, REF 9015A0011) into the gastrocnemius (medial and lateral head of the gastrocnemius, 100 units), the soleus (50 units), and the posterior tibial muscle (50 units). Group B (control group, n=12) patients received the same volume of placebo solution into the same number of injections of the same muscles. There was no other specific treatment other than the injections. Both groups received comprehensive rehabilitation. This included physiotherapy (45 minutes every workday) and occupational therapy (30 minutes every workday). Gait training was also performed. The therapy combined elements of the neurodevelopmental technique and motor relearning program.

The outcome measures were evaluated at weeks 0 (baseline), 4, and 8. Fugl-Meyer assessment (FMA) of the lower limbs, modified Ashworth Scale (MAS) assessment of the lower limbs, surface electromyography (sEMG), and the modified Barthel index (MBI), were assessed. At the end of the research, we also performed a gait analysis (step length, cadence,speed) and 6-min walking test in every patient. Muscle tone was assessed with the help of the MAS scores (0–4). The MAS is widely used for the assessment of muscle tone and spasticity in the lower limbs[15, 16]. Investigators were trained in the procedures to assess the MAS ankle score. Patients were assessed in the prone position and knee extension. The ankle was examined at the edge of an examination table and from maximal plantar flexion through to maximal dorsal flexion for the MAS ankle score. None of the patients had contracture or joint ankylosis, which would limit ROM. Lower-limb motor control was assessed with the help of the Fugl-Meyer motor score (0–34). Surface EMG electrodes were placed over the lateral and medial gastrocnemius. Where available, guide lines written by the Surface Electromyography for the Non-Invasive Assessment of Muscles group were adopted for the surface electromyography procedures[17]. The starting position for all ankle assessments was the prone position and knee extension. The ankle was initially moved from maximal plantar flexion through to maximal dorsal flexion. For the analysis of spasticity of the gastrocnemius, the average integrated sEMG levels were calculated during slow passive dorsiflexion of the ankle. We assessed every patient 3 times in each assessment and took the average value.

Table 1. Subject demographic data

	Treatment group	Control group
n	11	12
Gender (male/female)	7/4	8/4
Age, years	55±12	58±14
Stroke interval, days	24.2±12.2	23.2±17.2
Diagnosis		
Ischaemic /hemorrhagic	6/5	7/5
Barthel Index (0–100)	32.1±5.3	30.1±.1
LEMI score	5.52±1.7	5.83±1.19

Results are presented as the mean ± SD.

The SPSS 14.0 software was used for the statistical analyses. Descriptive summary statistics for differences between the mean scores and mean change from baseline (SD) for all other secondary measures are presented. Within-group and between-group comparisons were carried out using, respectively, paired and independent t-tests. Dichotomous variables were analysed using χ^2 tests. A Kruskal-Wallis test was initially carried out on the baseline data to test for any differences between the two groups. The level of statistical significance was set as $p<0.05$.

RESULTS

The clinical and demographic data at baseline were comparable (Table 1). Twenty-three patients completed the study. Side effects did not occur during the research. The gait analysis, FMA, and MBI results were significantly improved in both groups. FMA and MBI in the treatment group were better than in the control group in week 8 ($p<0.05$, Table 2). The change in the level of spasticity as assessed by sEMG activity during slow passive stretch from baseline to the final follow-up is also shown in Table 2. A decrease in the mean levels of gastrocnemius activity therefore indicates a reduction in spasticity in the treatment group ($p<0.05$, Table 2).

The step length, cadence, speed, and 6-min walking distance of the treatment group were better than those of the control group ($p<0.05$, Table 3).

At the end of the research, the MAS scores in the BTX-A treatment group were lower than those in the control group ($p<0.05$, Table 4).

Table 2. The changes in FMA, MBI, and sEMG level (mV) in the treatment group and control group in weeks 0, 4 and 8

	Treatment group (n=11)	Control group (n=12)
Barthel Index (0–100)		
Week 0	38.8±7.7[a]	37.5±5.9[b]
Week 4	44.1±9.8	40.9±11.5
Week 8	65.5±9.5[ae]	50.1±11.8[be]
Fugl-Meyer assessment (0–34)		
Week 0	22.5±5.1[c]	21.1±4.1[d]
Week 4	25.1±7.5	24.4±5.4
Week 8	29±3.3[cf]	27.8±5.5[df]
sEMG level (μV) of gastrocnemius		
Week 0	21.8±6.9	19.9±7.1
Week 4	15.8±7.8[g]	26.8±9.1[g]
Week 8	14.1±7.7[h]	29.9±8.4[h]

Results are presented as the mean ± SD. [a,b,c,d]$p<0.05$, self-matching test for MBI and FMA, compared before and 8 weeks later. [e,f]$p<0.05$, comparison of MBI and FMA between the treatment and control groups at week 8. [g,h]$p<0.05$, comparison of the sEMG levels (μV) of the gastrocnemius between treatment and control groups at weeks 4 and 8.

Table 3. The changes in step length, cadence,speed, and 6-min walking distance in the treatment groups and control group in week 8

	Treatment group (n=11)	Control group (n=12)
Step length (cm)	103.8±9.8[a]	69.9±7.7[a]
Cadence (steps/min)	82.6±8.1[b]	77.2±5.5[b]
Speed (cm/s)	112.5±11.5[c]	89.3±17.1[c]
6-min walking distance (m)	398.9±22.7[d]	322.7±37.6[d]

Results are presented as the mean ± SD. [a,b,c,d] $p<0.05$, comparison of step length, cadence, speed and 6-min walking distance between the treatment and control groups at week 8.

Table 4. Modified Ashworth Scale scores in both the treatment and control group

	Modified Ashworth Scale scores					
	0	1	1+	2	3	4
Treatment group (n=11)	0	7	3	1	0	0
Control group (n=12)	0	0	3	5	4	0

Comparison of muscle tone by MAS between the treatment and control groups at week 8 (χ^2 tests, $p<0.05$).

DISCUSSION

The aim of this study was to investigate whether an early lower-limbs injection of botulinum toxin A (BTX-A) in patients within 4–6 weeks after stroke could help prevent disabling muscle stiffness and walking dysfunction 8 weeks later. Our findings suggest that early BTX-A treatment significantly reduces muscle tone (MAS domain), improves gait, and improves locomotion ability (gait analysis and FMA domain); also, the treatment had an impact on satisfaction with respect to participation and quality of life (MBI domain).

The incidence of poststroke spasticity ranges from 17% to 38%, with 4–9% of patients from disabling spasticity[18]. Patients with spasticity can suffer from impaired walking ability that includes equinus foot; consequently, this disability negatively affects performance of the patient's activities of daily living (ADL). Clinically evident spasticity does not usually become a problem within the first month after a stroke[3], but patients with initially severe limb paresis are at higher risk for developing spasticity[8–11]. Our data suggests that sEMG evidence of spasticity is present even at this early stage (Table 2). This finding is in agreement with a study that evaluated the early development of spasticity in a severely impaired population[19]. A neurolytic agent lessened the spasticity-related intermittent or sustained involuntary muscle activity of the ankle flexors, so that the joints were held in a less fixed position. This also again might have delayed and/or diminished the subsequent contracture development, resulting in reduced muscle stiffness at follow-up. Cosgrove reported that the intramuscular injection of BTX-A prevented the development of contractures[20].

Subacute stroke patients would benefit from early BTX-A injection. It would reduce the degree of spasticity in lower limb muscles. It also provides a valuable time window for patients to receive the therapy, which is concentrated on mobilization of the lower extremity joints in conjunction with tone-inhibiting and facilitating manoeuvres. We speculated that an early lower-limb BTX-A injection in subacute stroke patients with a nonfunctional lower extremity (defined as a LEMI < 10) might improve their functional outcome. It may be that by changing the time course of spasticity development, the functional outcome may have been influenced. While this could stem directly from the botulinum toxin, an altered time course of spasticity may have allowed for improved effectiveness of therapy during the acute rehabilitation period.

In our study, the dose injected was lower than that in a previous study[21]. Kaji reported that a 300 iu BTX-A injection will obviously decrease the degree of spasticity[22]. In our group, the patients (experimental group, n=11) who received the 200 iu BTX-A injection also obtained the same effect. It may be that by preventing spasticity development and providing a time window for rehabilitation, the earlier BTX-A injected, the lower dose will be used. Possible improvement of equinus foot after BTX-A treatment in combination with rehabilitation is expected to allow correction of walking patterns reduce the systemic burden of walking. Increasing walking distance (or decreasing time required for a given walk) may expand the range of patient activities and lead to improved ADL. These results confirmed the safety and effectiveness of BTX-A and that it was useful in improving rehabilitative treatment of subacute poststroke lower-limb spasticity. Early low dose BTX-A injection in subacute stroke patients may reduce spasticity, improve gait, and daily living abilities.

The limitation of the study is obvious: the number of patients is small. The long-term efficacy and safety and the effects on rehabilitation of early BTX-A injection will be evaluated using data obtained in more patients. We also should perform further research to find the optimal dose of BTX-A for subacute stroke patients.

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