BRIEF COMMUNICATION

Effects of Onabotulinum Toxin A on Gait in Parkinson's Disease Patients with Foot Dystonia

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ABSTRACT: We investigated the effects of botulinum toxin on gait in Parkinson's disease (PD) patients with foot dystonia. Six patients underwent onabotulinum toxin A injection and were assessed by Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS), visual analog scale (VAS) of pain, Timed Up and Go (TUG), Berg Balance Test (BBT), and 3D gait analysis at baseline, 1 month, and 3 months. BFMDRS ($p = 0.002$), VAS ($p = 0.024$), TUG ($p = 0.028$), and BBT ($p = 0.034$) were improved. Foot pressures at Toe 1 ($p = 0.028$) and Midfoot ($p = 0.018$) were reduced, indicating botulinum toxin's effects in alleviating the dystonia severity and pain and improving foot pressures during walking in PD.

RÉSUMÉ : Effets de la toxine botulique de type A sur la démarche de patients atteints de la maladie de Parkinson et aux prises avec des symptômes de dystonie du pied. Nous nous sommes penchés sur les effets de la toxine botulique de type A (*onabotulinum toxin A*) sur la démarche de patients atteints de la maladie de Parkinson (MP) et aux prises avec des symptômes de dystonie du pied. Six patients ont donc bénéficié d'injections de toxine botulique de type A et ont été évalués ensuite à l'aide des outils suivants : l'échelle d'évaluation de la dystonie de Burke Fahn-Marsden (EEDBFM), l'échelle visuelle analogique (EVA) de la douleur, le test *Timed Up and Go* (TUG), l'échelle d'évaluation de l'équilibre de Berg (EEEB) ainsi que l'analyse en 3 dimensions de la démarche (au début de cette étude, au bout d'un mois et au bout de 3 mois). Les résultats obtenus à l'EEDBFM ($p = 0{,}002$), à l'EVA ($p = 0{,}024$) et aux tests TUG ($p = 0{,}028$) et EEEB ($p = 0{,}034$) ont ainsi montré une amélioration. À noter aussi que la pression exercée sur le gros orteil (*toe 1*) ($p = 0{,}028$) et le pied moyen ($p = 0{,}018$) a été réduite chez ces patients, ce qui indique que la toxine botulique de type A parvient à atténuer la gravité de la dystonie et la douleur mais aussi à améliorer la pression exercée sur les pieds au moment où ces patients parkinsoniens marchent.

Keywords: Parkinson's disease, Foot dystonia, Botulinum toxin A, Gait

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Dystonia occurs in at least 38% patients with Parkinson's disease (PD),[1] and it involves many body regions, especially the foot. Foot dystonia causing pain and deficits in foot posture increases walking difficulties and falling risks in PD. Botulinum neurotoxin (BoNT) injection was shown to have reduced the pain and severity of lower limb dystonia.[2] A recent study of foot dystonia revealed improved gait velocity in PD after BoNT treatment.[3] However, BoNT's effects on gait and foot pressure were still unclear. Thus, our aim was to investigate its impacts on gait and foot pressure in PD with foot dystonia.

Six PD patients with foot dystonia, causing pain and difficulty in walking, were recruited into the study. Diagnosis of PD was performed according to the Movement Disorders Society (MDS) diagnostic criteria by at least two neurologists skilled in movement disorders. The study was approved by the ethics committee of Ruijin Hospital, Shanghai Jiaotong University School of Medicine. All participants provided written informed consents. Inclusion criteria were age in the range of 18–80 years, bilateral or unilateral foot dystonia (inversion, plantar, and toe flexion) inducing walking difficulties for at least 1 h per day with duration ≥1 year, failing to respond to common pharmacotherapy for dystonia, no change in the antiparkinsonian treatment for at least 3 months prior to and during the study, no other associated organic or psychiatric disorders, and no history of treatment with BoNT injection or lower limb surgery. Exclusion criteria included atypical parkinsonian syndromes, foot dystonia associated with dopaminergic drugs, contraindication to BoNT injection, dementia, and rheumatoid arthritis patients.

Foot postures of six patients were presented as plantar and toe flexion with/without inversion. Six lower limbs muscles were chosen according to the form of foot dystonia: tibialis posterior (TP), gastrocnemius medialis (GM), flexor digitorum longus (FDL), flexor digitorum brevis (FDB), flexor hallucis longus

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Table 1: Effects of botulinum toxin A injection on dystonia and gait characteristics

Measures	Mean ± SD	Mean change from baseline (95% CI)	p-Value
†VAS score			
Baseline	3.00 ± 0.63		
1 month	1.33 ± 0.52	−1.67 (−2.21, −1.12)	0.023*
3 months	1.50 ± 0.55	−1.50 (−2.07, −0.93)	0.024*
†BFMDRS total score			
Baseline	10.17 ± 3.13		
1 month	3.67 ± 2.16	−6.50 (−10.17, −2.83)	0.001*
3 months	4.33 ± 1.51	−5.83 (−9.50, −2.16)	0.002*
†BFMDRS movement score			
Baseline	7.12 ± 2.86		
1 month	2.17 ± 0.98	−5.00 (−8.25, −1.75)	0.026*
3 months	2.67 ± 1.03	−4.50 (−7.60, −1.40)	0.027*
†BFMDRS disability score			
Baseline	3.00 ± 0.63		
1 month	1.50 ± 1.38	−1.50 (−3.05, 0.05)	0.059
3 months	1.67 ± 0.82	−1.33 (−2.88, 0.21)	0.104
†TUG (s)			
Baseline	14.06 ± 7.82		
1 month	13.01 ± 6.92	−1.05 (−2.63, −0.53)	0.028*
3 months	13.30 ± 7.17	−0.76 (−2.00, −0.48)	0.028*
†BBT score			
Baseline	49.00 ± 9.42		
1 month	50.17 ± 8.86	1.17 (0.38, 1.96)	0.038*
3 months	50.00 ± 9.25	1.00 (0.34, 1.67)	0.034*
†Stride length (cm)			
Baseline	93.00 ± 37.46		
1 month	95.00 ± 21.74	2.00 (−16.16, 20.16)	0.786
3 months	95.50 ± 26.17	2.50 (−11.43, 16.43)	0.893
Gait velocity (cm/s)			
Baseline	81.05 ± 38.88		
1 month	85.33 ± 31.44	4.28 (−7.16, 15.73)	0.380
3 months	84.00 ± 37.07	2.95 (−3.62, 9.52)	0.300
Foot forces (n)			
†Toe 1			
Baseline	98.15 ± 76.07		
1 month	48.83 ± 36.19	−49.32 (−91.75, −6.88)	0.012*
3 months	55.35 ± 49.60	−42.80 (−70.78, −14.82)	0.028*
Toe 2–5			
Baseline	8.52 ± 7.86		
1 month	16.23 ± 7.47	7.72 (−2.07, 17.50)	0.098
3 months	13.83 ± 5.07	5.32 (−3.20, 13.83)	0.169
Meta 1			
Baseline	91.62 ± 56.74		
1 month	93.53 ± 57.10	1.92 (−60.38, 64.21)	0.940
3 months	88.42 ± 49.06	−3.20 (−50.59, 44.19)	0.869

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Table 1: *(Continued)*

Measures	Mean ± SD	Mean change from baseline (95% CI)	p-Value
Meta 2			
Baseline	158.50 ± 70.13		
1 month	145.35 ± 49.96	−13.15 (−64.34, 38.04)	0.538
3 months	147.52 ± 57.85	−10.98 (−40.32, 18.36)	0.380
Meta 3			
Baseline	208.37 ± 64.69		
1 month	148.43 ± 66.52	−59.93 (−190.43, 70.56)	0.291
3 months	171.70 ± 42.68	−36.67 (−122.83, 49.50)	0.324
Meta 4			
Baseline	187.10 ± 105.37		
1 month	117.15 ± 44.67	−69.95 (−181.37, 41.47)	0.167
3 months	135.63 ± 50.85	−51.47 (−124.83, 49.50)	0.324
Meta 5			
Baseline	199.08 ± 181.26		
1 month	95.15 ± 102.01	−103.93 (−222.41, 14.54)	0.074
3 months	113.03 ± 111.52	−86.05 (−192.66, 20.56)	0.093
Midfoot			
Baseline	226.53 ± 119.69		
1 month	108.48 ± 74.75	−118.05 (−195.80, −40.30)	0.011*
3 months	140.55 ± 78.22	−85.98 (−149.84, −22.13)	0.018*
Heel medial			
Baseline	226.90 ± 31.69		
1 month	229.23 ± 33.54	2.33 (−84.23, 88.89)	0.947
3 months	225.87 ± 37.72	−1.03 (−66.06, 63.99)	0.969
Heel lateral			
Baseline	205.67 ± 92.01		
1 month	159.68 ± 43.54	−45.98 (−149.37, 57.40)	0.305
3 months	182.02 ± 46.48	−23.65 (−121.22, 73.92)	0.561

VAS = visual analog scale; BFMDRS = Burke–Fahn–Marsden Dystonia Rating Scale; TUG = Timed Up and Go; BBT = Berg Balance Test; Toe 1 = Hallux; Meta = metatarsal.
*$p < 0.05$.
†Non-normal distribution.

(FHL), and flexor hallucis brevis (FHB). Electromyographic stimulation was used to guide injection. The injection doses were as follows: TP 50–70U, GM 30–50U, FDL 40–50U, FDB 10–20U, FHL 40–50U, and FHB 10–20U. Onabotulinum toxin A was diluted with 2.0 ml of 0.9% saline to obtain a concentration of 50.0 U/ml.

Demographic and clinical features, including Unified Parkinson's Disease Rating Scale-III (UPDRS-III), Hoehn–Yahr (H-Y) Scale, L-dopa equivalent daily dose (LEDD), Hamilton Anxiety (HAMA) and Depression Scale-17 (HAMD-17), 39-item Parkinson's disease Questionnaire (PDQ-39), and Mini-mental State Examination (MMSE) were acquired at baseline. Dystonia severity and pain were measured by Burke–Fahn–Marsden Dystonia Rating Scale (BFMDRS) and visual analog scale (VAS). Timed Up and Go (TUG) and Berg Balance Test (BBT) were used to measure gait and balance function. Three-dimensional gait analysis system Vicon (Vicon T40 10 cameras, UK) and Footscan® platform system (Rsscan 3D plate 2m, Italy) were used to analyze the gait spatiotemporal parameters and foot pressure during walking.[4,5] Measurements were performed at baseline, 1 month, and 3 months after BoNT-A injections, respectively. All assessments were performed on medication with stable antiparkinsonian treatment for at least 3 months prior to and during the study.

Statistical analysis was performed using SPSS Statistics 21.0 software. The normal distribution of data was examined by the Kolmogorov–Smirnov test. Analysis of variance of repeated measurement was used for normally distributed data, while

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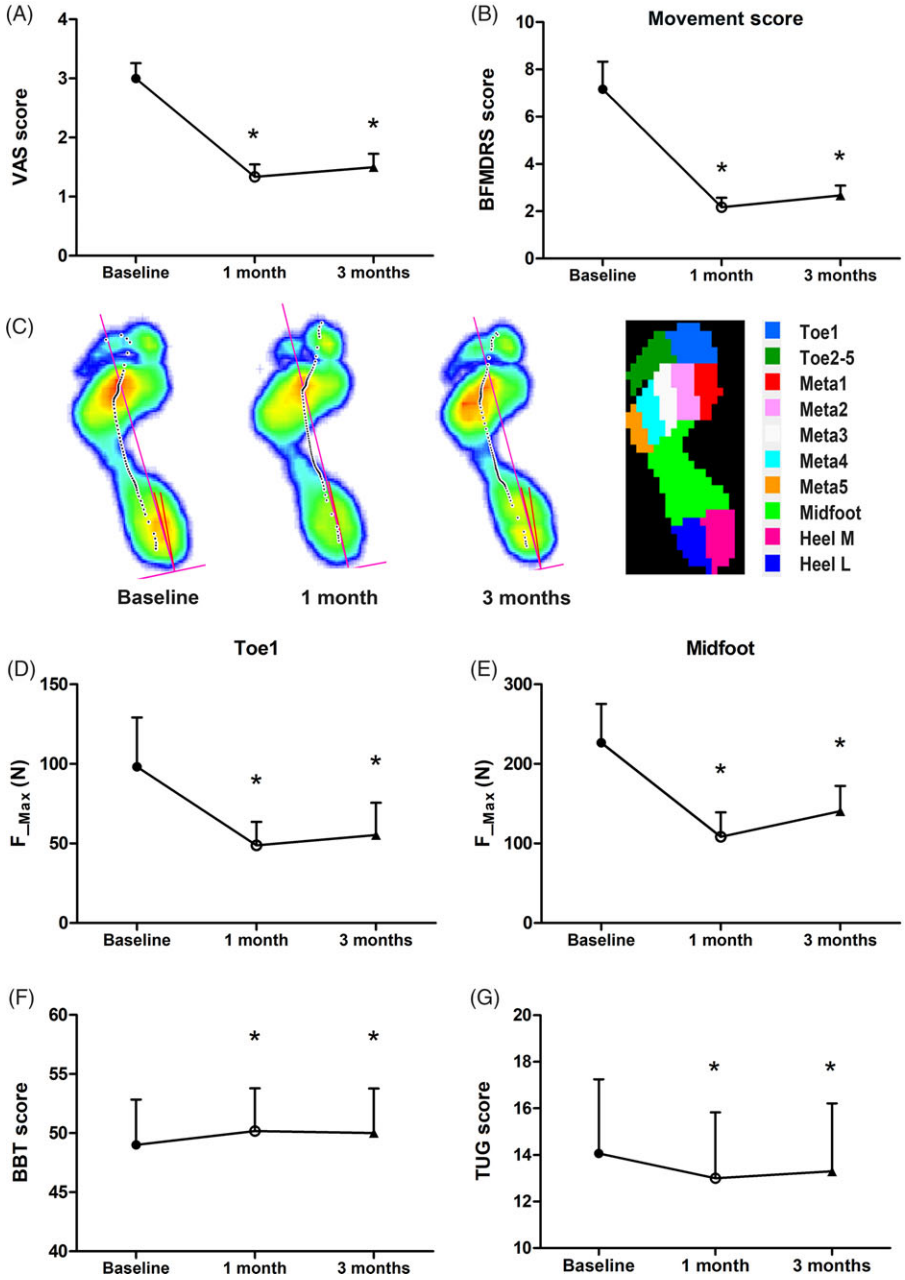

Figure 1: *Effects of botulinum toxin A injection on dystonia and gait characteristics. (A) VAS score was significantly reduced after BoNT-A injection; (B) BFMDRS movement score was significantly improved after BoNT-A treatment; (C) the right showed the 10-zone division of local foot, the left showed medial shift of the COP trajectory after BoNT-A therapy; (D) foot pressure at Toe 1 of the dystonic side was significantly reduced after BoNT-A injection; (E) foot force at Midfoot of the dystonic side was greatly relieved after BoNT-A treatment; (F) BBT score was greatly improved after BoNT-A therapy; (G) TUG score was greatly improved after BoNT-A therapy. *Significant differences. COP = center of pressure.*

generalized linear model was used for nonparametric analysis with Bonferroni multiple corrections. $p < 0.05$ were considered statistically significant.

Demographic and clinical features were listed in Supplementary Table 1. BoNT-A injection significantly decreased the BFMDRS scores (total score: 1 month vs. baseline, $p = 0.001$; 3 months vs. baseline, $p = 0.002$, and movement score: 1 month vs. baseline, $p = 0.026$; 3 months vs. baseline, $p = 0.027$) and pain associated with dystonia (1 month vs. baseline, $p = 0.023$; 3 months vs. baseline, $p = 0.024$) (Table 1 and Figure 1A and B). No local or distant side effects were reported by patients.

BoNT-A injection did not show significant effect on the gait (stride length: 1 month vs. baseline, $p = 0.786$; 3 months vs. baseline, $p = 0.893$, and gait velocity: 1 month vs. baseline, $p = 0.380$; 3 months vs. baseline, $p = 0.300$, Table 1), but the modification of the foot axis (Figure 1C) showed that the plantar center of pressure

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(COP) trajectory was shifted medially during walking after the injection. Comparisons between baseline and 1 month after BoNT-A treatment (Table 1 and Figure 1D and E) showed significant reduction in foot pressures at Toe 1 ($p = 0.012$) and Midfoot ($p = 0.011$) of the dystonic foot, and significant changes were consistently found at 3 months (Toe 1, $p = 0.028$; Midfoot, $p = 0.018$).

Balance ability evaluated by BBT (1 month vs. baseline, $p = 0.038$; 3 months vs. baseline, $p = 0.034$) and TUG (1 month vs. baseline, $p = 0.028$; 3 months vs. baseline, $p = 0.028$) were significantly improved after injection (Table 1 and Figure 1F and G).

This study demonstrated that BoNT-A injection could relieve the spasms of foot muscles and the degree of pain associated with dystonia in PD. VAS and BFMDRS scores of the lower limbs were reduced after BoNT-A injection. These results were consistent with a previous study,[3] indicating BoNT-A injection as a useful therapy for improving pain and dystonia severity of foot dystonia. Furthermore, improvement in foot pressure distribution and balance ability were also observed.

Plantar pressure is the pressure that acts between the foot and the support surface, which is related to gait stability and balance. However, previous studies exploring the effect of BoNT-A on foot dystonia did not focus on the change of plantar pressure, and our study is the first to evaluate its impact on foot pressure. Compared to normal values for foot pressure of 24 age-matched (58.71 ± 6.18) healthy controls from our center, patients presented that midfoot was under the most pressure, while normal foot pressure distribution followed such order as Heel medial>Heel lateral>Meta 1–5>Midfoot>Toe (Supplementary Table 2 and Supplementary Figure 1). The major distribution of plantar pressure between heel and metatarsal plays an important role in supporting the body to ensure normal walking and balance.[6] Foot problems with impaired plantar pressure distribution could increase the risk of falling related to higher plantar pressure and decreased stability.[6] Hallux and midfoot pressure were significantly reduced, and patients exhibited similar foot pressure distribution to normals after BoNT-A therapy. In addition, plantar COP during gait, which has been used to predict risk of injury, was shifted medially after treatment, indicating decreased risk for future falls.[7]

We recorded UPDRS-II item 13 (falls) and found only patient NO. 3 scored 2 at baseline and it was reduced to 1 score one month after BoNT-A injection. However, the other five patients did not reported falls during the study. This might be due to the mild disability and early stage of the PD patients (H-Y 1.5–2). Although we only found limited changes in falls, improved balance ability after BoNT-A treatment was reflected by BBT and TUG.

Effects of BoNT-A injection on spatiotemporal gait parameters were also analyzed, but no improvement was found in stride length and gait velocity. It might be confusing that the improvements in TUG did not translate into an improvement of gait velocity, but TUG assesses gait-related activities which involve dynamic stability,[8,9] providing more information than straight-line gait. It indicated that balance capacity was more likely to be improved rather than just walking speed after BoNT-A treatment.

However, Gupta et al. found improvement of gait velocity and stride length in six PD patients treated by deep brain stimulation (DBS) after botulinum toxin injection.[10] They also showed consistent results in their later study of 14 patients with foot dystonia (including 5 PD-DBS, 5 PD, and 4 foot dystonia).[3] The inconsistent results with our study might be attributed to the different phenotypes of enrolled participants. We mainly included early-stage PD patients with relatively mild foot dystonia (H-Y 1.5–2), while the other two studies recruited advanced PD patients with severe foot dystonia (H-Y ≥ 2), which might have led to a type II error. Further studies of advanced PD patients with foot dystonia are needed to verify this hypothesis. The limitations of this study also include the small sample size and no placebo control.

In conclusion, the results of our study indicate that botulinum toxin injections not only alleviated the severity of dystonia and pain related to foot dystonia but also improved the plantar pressure distribution and balance ability in PD patients. Further confirmation through a larger-scale, randomized controlled trial is warranted.

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Disclosures

The authors have no conflicts of interest to declare.

Statement of Authorship

Y-WW, JL, and SDC conceived and supervised the project. PH and Y-YL contributed to patients' assessment and drafted the manuscript. PH performed data management and statistical analyses. JEP edited and finalized the manuscript. QX, YW, and SC contributed to patients' recruitment. All authors read and approved the final version of the manuscript.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.42.

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