

Botulinum Toxin for Pisa Syndrome: An MRI-, Ultrasound- and Electromyography-guided Pilot Study

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ABSTRACT

INTRODUCTION: Pisa syndrome is a disabling, medication-resistant, postural abnormality that may affect 7-10% of patients with Parkinson's disease. In this study, we sought to assess the efficacy of botulinum toxin injections in Parkinson's disease-associated Pisa syndrome using a Magnetic Resonance Imaging-, Ultrasonography-, and Electromyography-guided combined approach.

METHODS: We conducted a pilot study to evaluate the efficacy of botulinum toxin type-A injection in paraspinal and non-paraspinal axial muscles after a Magnetic Resonance Imaging and ultrasound-guided electromyography evaluation. Inclusion criteria were Pisa syndrome, idiopathic Parkinson's disease, and stable dopaminergic medications. Exclusion criteria were previous treatment with botulinum toxin, history of major spine surgery, and severe orthopedic diseases. As primary endpoint, we measured the rate of patients improving by at least 5° in the lateral trunk flexion 2 months after therapy. Secondary endpoints were the extent of lateral trunk flexion improvement, and changes in PS-associated pain/discomfort, measured by the Visual Analogue Scale.

RESULTS: Out the 15 patients initially enrolled, 13 completed the follow-up assessment, while 2 joined a rehabilitation program and were excluded from the analyses. The rate of responders was 84.6% (n= 11/13), with 40% average reduction in trunk bending. Pain/discomfort improved in all patients, with 52.2% amelioration at the Visual Analogue Scale. The procedure was well tolerated in all cases, without side effects or complications.

CONCLUSION: A combined imaging and EMG botulinum toxin approach to Pisa syndrome may yield a success rate greater than 80% in Parkinson's disease.

1. INTRODUCTION

Pisa syndrome (PS), defined as a lateral trunk flexion that improves with passive mobilization and supine positioning [1], is an acquired postural abnormality observed in 7.4% - 10.3% of patients with Parkinson's disease (PD).

The clinical management of PS might be challenging. While the response to levodopa is usually minimal or absent [2], dopamine-agonists, cholinesterase inhibitors, or neuroleptics may have a detrimental effect or even precipitate the severity of PS in predisposed subjects [1]. Promising data have been reported in PS patients treated with Botulinum toxin (BoNT) injections. The clinical experience, however, remains limited to small sample size studies and single case reports not providing a systematic assessment of the target muscles [3-6]. New insights provided by neurophysiological studies documenting the involvement of diverse groups of muscles, characterized by different patterns of muscle hyperactivation, may explain the low rate of responders in previous reports assessing the BoNT efficacy in PD patients with PS [3,4].

We used a combined Magnetic Resonance Imaging (MRI)-, Ultrasonography (US)-, and Electromyography (EMG)-guided approach to ensure the maximal accuracy in the treatment of PD-associated PS with BoNT injections.

2. MATERIALS AND METHODS

2.1 Study population

In this prospective, pilot study 15 consecutively consenting PD patients with PS were recruited from the Movement Disorders Unit of the University of Torino (Italy) between December 2015 and September 2017.

Inclusion criteria were idiopathic PD, as per the UK Brain Bank criteria [7]; PS, defined as a lateral trunk flexion of at least 10° improved by passive mobilization and

supine positioning [1]; and stable dose of dopaminergic medications for at least 4 weeks prior the enrollment.

Exclusion criteria were previous treatment with BoNT injection, history of major spine surgery, and severe spine orthopedic diseases, including vertebral fractures, spondylodiscitis, and idiopathic scoliosis with vertebral rotation.

2.2 Endpoints

Our primary endpoint was to evaluate the rate of responders, defined as the number of patients receiving an objective, clinically meaningful postural improvement 2 months after BoNT injection. In the absence of validated criteria for defining a clinically meaningful response to treatment in patients with PS, we relied on previous literature [4], and set a cut-off of 5° to define a significant improvement in the lateral bending. Therefore, as primary endpoint, we assessed the rate of responders, defined as the number of patients improving by at least 5° in the lateral trunk flexion.

Changes in the lateral trunk flexion, defined as the angle between (a) the vertical axis and (b) a line connecting the fulcrum of the bent spine with the 7th spinous process (Figure 1), were calculated from planar view pictures of the patient standing in front of a wall goniometer using “ImageJ”, an open source image processing program developed by the National Institute of Health and validated for posture analysis [2]. Pictures were analyzed by an operator blinded to the two study conditions, namely T0 (baseline, before BoNT injection), and T1 (follow-up, 2 months after BoNT injection). No changes were allowed in dopaminergic medications for the entire duration of the study. Patients enrolling in programs of physical therapy were excluded from the analysis.

As secondary analyses, we evaluated the improvement in PS-associated

pain/discomfort on a VAS score of 0 to 10. Procedure-related adverse events (AEs) and side effects were collected and classified as per the FDA guidelines [8] at T0, during and till 1 hour after the treatment, and at T1.

2.3 Procedure

2.3.1 Phase 1: Morphological evaluation of axial muscles using T1-weighted MRI images

T1-weighted axial MRI (1.5 Tesla) sequences of the thoracic and lumbar spine were used to assess atrophy of paraspinal and non-paraspinal axial muscles, which is a sensitive marker of muscular involvement in PD-associated PS [9]. A visual comparison between ipsilateral and contralateral muscle areas was performed to identify hypertrophy and atrophy in the paraspinal muscles (longissimus thoracis, iliocostalis lumborum, and spinalis dorsi) at L2-L4 level, and in the non-paraspinal muscles (internal and external abdominal oblique, and iliopsoas). In addition to the visual assessment, muscle atrophy was evaluated according to the extent of fatty degeneration (T1-weighted hyperintensity) and rated as moderate ($\leq 50\%$) or severe ($> 50\%$) according to the methodology described by Mercuri and colleagues [10].

2.3.2 Phase 2: Functional evaluation of axial muscles using a US- and EMG-guided approach

A functional assessment of the target muscles was carried out using an US- (Esaote, MyLab™) and EMG-guided (Dantec® Keypoint® G4 Workstation) approach to evaluate muscle groups predominantly involved in the pathogenesis of the PS: paraspinal muscles (longissimus thoracis, iliocostalis lumborum, and spinalis dorsi) at L2-L4 level and non-paraspinal muscles (internal and external abdominal oblique, and

iliopsoas) [9,11].

EMG assessments were carried out using a concentric 26 or 23 gauge single-use needle connected to a multichannel amplifier (1,000x gain), band-pass filtered at 300 – 3,000 Hz, and sampled at 10,000 Hz, in the two following conditions: lying down on an examination table (prone on the examination table with arms along the trunk), and after standing. Muscle hyperactivity was defined as the persistence of motor unit potential (MUP) during activation of antagonist muscle groups with the following maneuver: the subject was asked to press down against the bed with the shoulder contralateral to the EMG explored paraspinal muscles [3]. Each muscle was assessed by visual inspection and rated on a scale of 0 to 3 as follows: 0 = rest firing pattern, 1 = single fiber firing pattern, 2 = transitional pattern, 3 = full interference pattern PS [13].

2.3.3 Phase 3: BoNT injection

OnabotulinumtoxinA (BoNT-A), dissolved as 100 units in 2 ml of saline, was injected under US and EMG guidance in muscles with: a) pathological muscular hyperactivity on EMG study when standing; and 2) absence of severe muscle atrophy on MRI imaging (Supplementary Figure 1). When muscular hyperactivity was observed bilaterally, the more active muscle was treated. When EMG in standing position was not performed or no asymmetry was found, the treatment was based on findings from the EMG performed in the lying position. Doses of BoNT-A ranged from 50 to 75 units for each paraspinal muscle injected, and from 25 to 50 units for each non-paraspinal muscle injected, based on the EMG abnormal activity rate and the experience of the neurophysiologist.

2.4 Statistical analysis

Continuous data were summarized as mean \pm standard deviation or percentages, as appropriate. The percentage of responders was calculated as the rate of patients reporting an improvement of at least 5° in lateral bending between T0 and T1. Change in the lateral trunk flexion and VAS score between T0 and T1 were analyzed using the nonparametric Wilcoxon signed-rank test.

All tests were two-tailed and considered a p-value < 0.05 as statistically significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS 22 for Mac, Chicago, IL).

The local institutional review board approved this study, and all patients gave their written informed consent to participate.

3. RESULTS

Out of the 15 patients treated with BoNT, 2 joined a rehabilitation program between T0 and T1 and were excluded from the analyses as per the study design (Supplementary Figure 1). Clinical and demographic characteristics of the 13 patients included in the analyses are reported in Supplementary Table 1.

3.1 Functional and morphological evaluation of axial muscles involved in PS abnormal posture

The MRI assessment detected an asymmetry of muscle trophism in 84.6% of paraspinal (n = 11/13), 61.5% of iliopsoas (n = 8/13), and 38.4% of abdominal (n = 5/13) muscles. All patients had a moderate ($< 50\%$) fatty degeneration in the paraspinal muscles, which was unilateral to the bending side in 69.2% (n = 9/13) and

bilateral in 30.8% (n = 4/13).

BoNT injections were performed in 92.3% (n = 12/13) of patients in the paraspinal muscles, ipsilateral to the bending side in 33.3% (n = 4/12) and contralateral to the bending side in 66.7% (n = 8/12). Abdominal muscles were injected in 38.5% (n = 5/13) of patients, ipsilateral to the bending side in 20% (n = 1/5), and contralateral to the bending side in 80% (n = 4/5). The iliopsoas was injected in 15.4% (n = 2/13) of patients, contralateral to the bending side in all cases. Data on EMG findings, sites, and doses of BoNT injection administered are reported in Table 1.

The average dose of BoNT-A used was 151.9 ± 53.5 units.

3.2 Primary and secondary outcomes

The rate of responders was 84.6% (n = 11/13). One patient did not improve his lateral trunk flexion, and 1 patient worsened. On average, the angle of lateral trunk flexion improved by 40% between T0 and T1 ($p < 0.001$), from 15.7 ± 8.4 to 9.4 ± 11.8 degrees (Supplementary Figure 2).

Pain/discomfort showed a 52.2% reduction in the total VAS score ($p < 0.001$), from 6.9 ± 2.2 to 3.3 ± 1.6 (Supplementary Figure 2).

All patients tolerated the procedure well. There were no intra- or peri-procedural AEs, sustained bleeding, or cutaneous reactions. No cases of therapy-related adverse effects were observed during the follow-up.

4. DISCUSSION

In this pilot study, we used a combined MRI-, US-, and EMG-guided approach to treat PD-associated PS with BoNT-A, observing a clinically significant improvement

in 84.6% of patients, with a 40% average reduction in the bending angle, and a 52.2% amelioration at the VAS score. There were no significant AEs or complications.

To the best of our knowledge, the current experience with BoNT in PD-associated PS is limited to 2 small trials and 2 case reports showing that BoNT may variably enhance the effect of programs for physical rehabilitation [3-6]. In this study, we decided to assess the effect of BoNT without the confounding effect of rehabilitation excluding, therefore, patients who joined programs of physical therapy during the study period.

Interestingly, we observed an extent of improvement similar or even greater than those reported by previous authors [3], suggesting that BoNT has an important effect on the functional outcome of PS, independently from the adjuvant effect of physical therapy. In addition, we exploited the major innovation of using a multimodal MRI-, US-, and EMG-guided approach for BoNT injections to ensure optimal targeting. Following the indications of recent EMG studies in patients with PS [9,12], we injected muscles with signs of pathological hyperactivity, regardless of whether they were ipsilateral or contralateral to the bending side. In fact, the pattern of functional alterations associated with PS can be multifaceted, with evidence of fatty degeneration and hyperactivity of paraspinal muscles located ipsilaterally, contralaterally, or even bilaterally to the bending side [12]. All the assessments were performed in standing and lying positions. The decision of which muscle to inject was based on the pattern of muscular hyperactivity observed in the standing position [4]. An MRI evaluation of muscle trophism was used to avoid injections in hypotrophic muscles ipsilateral to the bending side, which could have potentially worsened the lateral trunk bending. Despite this extensive assessment, one case failed to improve and another one worsened shortly after his treatment. A critical revision of data suggests that both cases might be, at least partly, associated with technical difficulties

in the differentiation between pathogenic vs. compensatory muscle hyperactivity.

Overall, we observed positive both objective and subjective improvements on the main measures of functional outcome, suggesting that a combined, multimodal, approach to BoNT injections in PD-associated PS may yield a success rate of 80%.

The strength of our conclusions, however, should be tempered by several limitations.

First, the absence of a control group to test the placebo effect, even though previous studies did not show any relevant placebo effects in PD patients with PS [3,4]; second, the relatively small number of patients enrolled in this pilot study, and third, the short-term duration of follow-up. Taking into account all of these limitations, our data support the notion that BoNT injections with an MRI-, US-, and EMG-guided approach can provide significant benefit in most PD patients with PS.

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Authors' Roles:

Carlo Alberto Artusi: study concept and design, analysis and interpretation of data, drafting of the manuscript.

Sara Bortolani: acquisition, analysis and interpretation of data, drafting of the manuscript.

Aristide Merola: critical revision of manuscript for intellectual content, revision of the statistical analysis.

Maurizio Zibetti: interpretation of data, critical revision of manuscript for intellectual content.

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FIGURE LEGENDS

Figure 1 – Example of measurement of the lateral trunk flexion

Example of measurement of the lateral trunk flexion angle in one patient before (left picture) and 2 months after BoNT-A injections (right picture).

Supplementary Figure 1 – Study flow chart

PD: Parkinson's disease

PS: Pisa syndrome

T0: baseline (before Botulinum toxin injection)

EMG: electromyography

MRI: magnetic resonance imaging

VAS: Visual Analogue Scale

T1: follow-up (2 months after Botulinum toxin injection)

Supplementary Figure 2 – Botulinum toxin injection outcomes

Baseline vs. follow-up changes in the angle degrees of lateral trunk flexion (A), and in the VAS score (B)

PS: Pisa syndrome

VAS: Visual Analogue Scale

Table 1 – EMG findings of asymmetric muscle activity and sites and doses of BoNT injection

	Side of trunk flexion	Side of muscle hyperactivity: Standing position		Side of muscle hyperactivity: Lying position		Muscles injected (BoNT units)	% reduction of lateral trunk flexion	% reduction of VAS
		Paraspinal	Non-paraspinal	Paraspinal	Non-paraspinal			
#1	Right	Left	Left	Left	Left	L longissimus (50), L iliocostalis (50), L int. abd. ob. (50)	80%	50%
#2	Left	Right	None	Left	Left	R longissimus (50), R iliocostalis (50), R spinalis (50)	13.2%	55.6%
#3	Right	Right	None	Right	None	R longissimus (50), R iliocostalis (50), R spinalis (50)	100%	60%
#4	Right	Left	Left	Left	Left	L longissimus (50), L iliocostalis (75), L int. abd. ob. (50), L ext. abd. ob. (50), L iliopsoas (25)	64.7%	40%
#5	Right	Left	Left	Right	None	L longissimus (75), L iliocostalis (75), L int. abd. ob. (50)	0%	42.9%
#6	Right	None	Left	None	Left	L int. abd. ob. (50), L iliopsoas (25)	100%	50%

#7	Right	Left	None	Right	Right	L iliocostalis (75), L spinalis (50)	100%	60%
#8	Right	N.A.	N.A.	Right	Right	R iliocostalis (50), R int. abd. ob. (50)	- 39.2%	25%
#9	Right	Left	None	Left	Right	L longissimus (50), L iliocostalis (50)	74.2%	40%
#10	Left	Right	None	Right	None	R iliocostalis (50), R spinalis (50)	50%	100%
#11	Right	Left	None	Right	None	L longissimus (75), L iliocostalis (75), L spinalis (50)	28%	33.3%
#12	Right	Right	None	Right	None	R longissimus (50), R iliocostalis (50), R spinalis (50)	73%	57.1%
#13	Right	Right	None	Right	None	R longissimus (75), R iliocostalis (75), R spinalis (75)	36.4%	40%

VAS = Visual Analogue Scale

N.A. = not available. In this patient EMG in standing position was not performed because of the pain caused by the prolonged standing position.

R = right

L = left

Figure 1 – Example of measurement of the lateral trunk flexion



Example of measurement of the lateral trunk flexion angle in one patient before (left picture) and 2 months after BoNT-A injections (right picture).

Supplementary Table 1 – Demographic and clinical data

Clinical/demographic data	Cohort (13 patients)
Gender (males - females)	10 - 3
Age (years)	70.5 ± 8.5
mean ± SD (range)	(66 - 78)
Age at PD onset (years)	60.0 ± 12.0
mean ± SD (range)	(36 - 74)
Age at PS onset (years)	66.0 ± 11.4
mean ± SD (range)	(44 - 77)
PS duration (years) ^a	2.7 ± 2.3
mean ± SD (range)	(0 - 7)
Pattern of PS onset ^b	2 acute, 2 subacute, 9 chronic
PS occurrence after PD diagnosis (months)	60.0 ± 70.1
mean ± SD (range)	(3-202)
Side of trunk deviation	2 right, 11 left
MDS-UPDRS part III total score	50.0 ± 10.1
mean ± SD (range)	(35-67)
Hoehn and Yahr score	3.0 ± 0.6
mean ± SD (range)	(2-4)
Use of dopamine-agonists	5 yes, 8 no
Levodopa Equivalent Daily Dose (LEDD)	850.4 ± 482.3
mean ± SD (range)	(300-2100)

PD = Parkinson disease

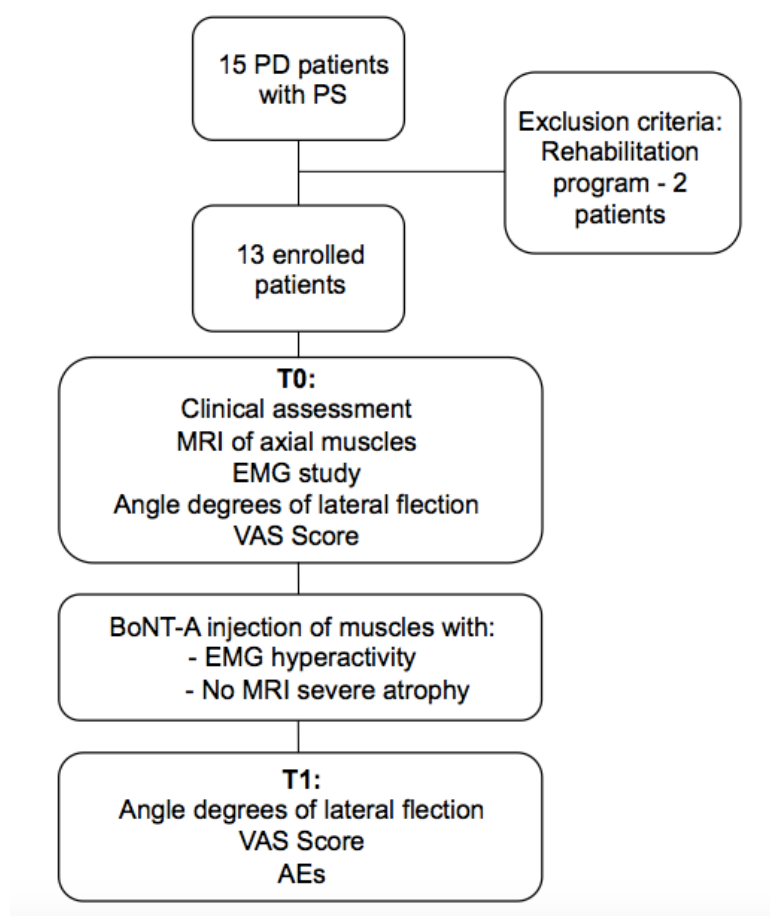
PS = Pisa syndrome

MDS-UPDRS = Movement Disorders Society Unified Parkinson's Disease Rating
Scale

^a time-frame between PS onset and BoNT injections

^b acute: < 1 month; subacute: 1-6 month; chronic: > 6 months

Supplementary Figure 1 – Study flow chart



PD: Parkinson's disease

PS: Pisa syndrome

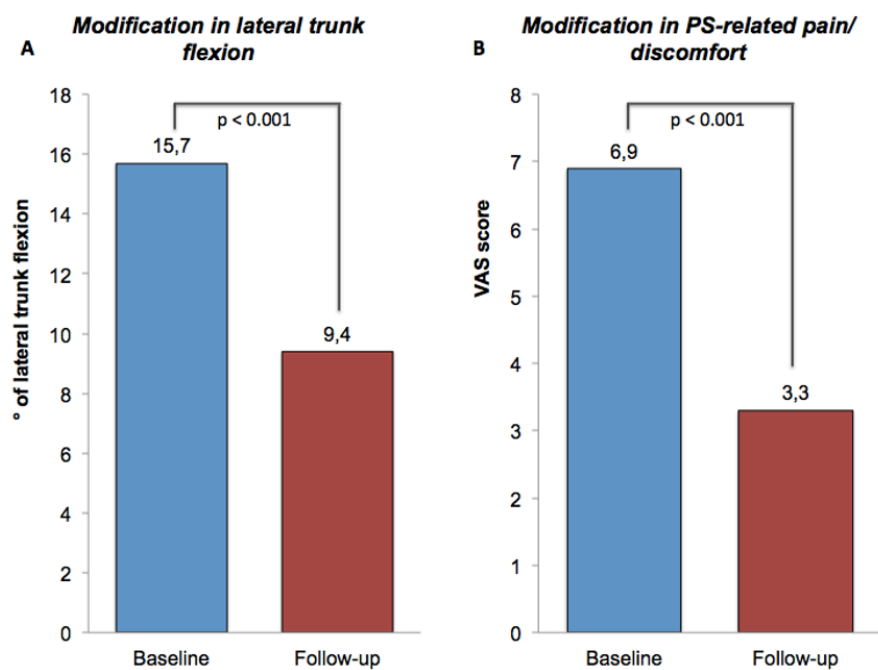
T0: baseline (before Botulinum toxin injection)

EMG: electromyography

MRI: magnetic resonance imaging

VAS: Visual Analogue Scale

T1: follow-up (2 months after Botulinum toxin injection)

Supplementary Figure 2 – Botulinum toxin injection outcomes

Baseline vs. follow-up changes in the angle degrees of lateral trunk flexion (A), and in the VAS score (B)

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