ORIGINAL ARTICLE

Botulinum Toxin Use in Refractory Pain and Other Symptoms in Parkinsonism

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ABSTRACT: ***Background:*** Parkinson's disease (PD) and other parkinsonian syndromes are chronic, progressive neurodegenerative diseases. With advancing disease, both motor and non-motor symptoms represent a considerable burden and symptom relief and quality of life improvement become the main goal of treatment. Botulinum toxins (BTX) are an effective treatment modality for many neurological conditions. ***Methods:*** To understand the potential usefulness of BTX in this population, we performed a retrospective chart review of all patients with a clinical diagnosis of idiopathic PD and atypical parkinsonism who received treatment with BTX injections in our center from 1995 to 2014 for a variety of symptoms. Response to BTX was assessed using a subjective Clinical Global Impression. ***Results:*** Records of 160 patients were reviewed. Probable idiopathic PD was the diagnosis in 117 patients (73.1%). The main indication for BTX treatment was pain (50.6% of cases). Other indications were the treatment of functional impairment resulting from dystonia (26.25%), sialorrhea (18.75%), freezing of gait, and camptocormia. Considering pain as indication, 81% of all patients with PD reported benefits after the first BTX injections. This benefit was maintained after the last recorded visit without significant difference in outcome compared with the first injection ($p = 0.067$). Similar results were observed in patients with atypical parkinsonism. ***Conclusions:*** Our results confirm the safety and efficacy of different uses of BTX in the symptomatic treatment of patients with parkinsonism even in advanced stages of the disease, and suggest BTX treatment could have a safe and useful role in the treatment of pain in this population.

RÉSUMÉ: Utilisation des toxines botuliniques pour soulager la douleur réfractaire et d'autres symptômes du parkinsonisme. ***Contexte:*** La maladie de Parkinson (MP) et les divers syndromes parkinsoniens sont des affections neuro-dégénératives chroniques et évolutives. Avec la progression de la maladie, tant ses symptômes moteurs que ses symptômes non-moteurs finissent par représenter un fardeau considérable. Le soulagement de ces symptômes et l'amélioration de la qualité de vie des patients deviennent alors le principal objectif d'un traitement. À cet égard, les toxines botuliniques (« BTX ») demeurent une modalité de traitement efficace dans le cas de nombreux troubles neurologiques. ***Méthodes:*** Afin de comprendre l'utilité potentielle des toxines botuliniques, nous avons procédé à un examen rétrospectif des dossiers de tous les patients qui, après avoir reçu un diagnostic de MP idiopathique et de syndrome parkinsonien atypique, ont bénéficié dans notre centre, de 1995 à 2014, d'un traitement par injection de toxines botuliniques pour toute une gamme de symptômes. La réponse à ces toxines a ensuite été évaluée au moyen de l'échelle Clinical Global Impression. ***Résultats:*** Nous avons passé en revue les dossiers de 160 patients. Des cas probables de MP idiopathiques ont été diagnostiqués chez 117 patients (73,1 %). Fait à noter, le soulagement de la douleur était le principal motif justifiant un traitement par injection de toxines botuliniques (50,6 % des cas). D'autres motifs étaient avancés : traiter un handicap fonctionnel résultant de la dystonie (26,25 %), la sialorrhée (18,75 %), des blocages (freezing of gait) et la camptocormie. Si l'on s'en tient à la douleur, 81 % des patients atteints de la MP ont signalé des bienfaits à la suite des premières injections de toxines botuliniques. Ces bienfaits ont perduré après leur dernière visite attestée, et ce, sans qu'on ait observé de différences significatives dans les résultats par rapport à la première injection ($p = 0{,}067$). Des résultats identiques ont été constatés chez des patients atteints d'un syndrome parkinsonien atypique. ***Conclusions:*** Nos résultats confirment à la fois la sécurité et l'efficacité des différents usages des toxines botuliniques dans le soulagement, même à un stade avancé, des symptômes de patients atteints de parkinsonisme. Ils suggèrent aussi qu'un traitement par injection de toxines botuliniques pourrait, sans danger, jouer un rôle utile dans le traitement de la douleur éprouvée par cette catégorie de patients.

Keywords: Parkinson disease, pain, palliative care, movement disorders

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Parkinson's disease (PD) and other parkinsonian syndromes, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS), are chronic, progressive neurodegenerative diseases. With advancing disease, both motor and non-motor symptoms represent a considerable illness burden and symptom relief and quality of life improvement become the main goal of treatment.

Botulinum toxins (BTX) are an effective treatment modality for spasticity and dystonia associated with neurological conditions. Case studies using BTX have suggested possible benefit for

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other symptoms associated with parkinsonism, including dystonia,[1] limb and jaw tremor,[2] apraxia of eyelid opening,[3] camptocormia,[4] dyskinesia,[5] freezing of gait,[6,7] sialorrhea,[8-10] overactive bladder,[11-13] and constipation.[3] However, to date, there are few randomized controlled trials using BTX evaluating these uses in parkinsonism. Thus, class I studies performed to date include three randomized controlled trials for the treatment of sialorrhea with different types of BTX,[8-10] one for the treatment of freezing of gait[7] and one for paratonia in patients with advanced cognitive impairment that showed a positive benefit on range of motion and reduce functional burden in this group of patients.[14]

To understand the potential usefulness of BTX in this particular population, we reviewed our experience more than 20 years of using BTX in our clinic for the treatment of a variety of symptoms associated with parkinsonism, including pain.

Methods

We performed a retrospective chart review of all patients with a clinical diagnosis of idiopathic PD[15] and atypical parkinsonism defined according to current criteria[16-18] who received treatment with BTX injections in our center from 1995 to 2014. Injections were performed by movement disorders specialists and trained fellows who also completed the patients' charts. With exception of those in the face muscles, all the injections were performed using electromyograph guidance. Information regarding diagnosis, gender, age (all variables collected at time of chart review unless otherwise stated), age of onset of the symptoms of the disease, disease duration, medications, indication for the use of BTX, time between the onset of the symptoms of the disease and the indication of BTX treatment, total dose/injection schedule, interval time between injections, and duration of the treatment were collected. Information regarding termination of the treatment was collected if available.

Response to BTX was assessed using a 5-point subjective Clinical Global Impression (CGI) retrospectively determined from clinical notes, according to patient and/or caregiver at last visit and recorded as 3 = very much improved, 2 = much improved, 1 = minimally improved, 0 = no change, and −1 = worse. This assessment was obtained after the first set of injections and in the last recorded visit. The difference in CGI between the first and the last BTX treatment was compared using the Wilcoxon signed-rank test. Significance was assigned $p < 0.05$. Logistic regression analysis was used to examine the effect of type of pain, location of the pain, BTX dose, and diagnosis on the response to the subjective response to the treatment. The presence of adverse effects was recorded where appropriate. Research ethics board approval was obtained.

Results

Records of 160 patients were reviewed. Probable idiopathic PD was the diagnosis in 117 patients (73.1%), 14 had probable PSP, 16 had probable MSA, 6 had probable CBS, and seven had otherwise unclassified Parkinsonism. Onabotulinum toxin A was used in 96% of the patients and incobotulinum toxin A in the other 4%. Demographics and the main indications for BTX treatment are shown in Table 1. Thirty-seven patients were attending the Movement Disorder Palliative Care clinic indicating an advanced disease (Hoehn and Yahr stage 3 or higher, presence of dementia,

Table 1: Demographics

								Indication for BTX				
	Number of patients	Sex (male)	Age of onset (mean ± SD)	Disease duration when BTX was started (years ± SD)	Number received STN DBS	Palliative care clinic	Pain	Functional disturbances from dystonia	Sialorrhea	Camptocormia	Freezing of gait	Tremor
PD	117	73	52 ± 12	13 ± 8	43	24	58	34	19	2	1	3
MSA	16	6	54 ± 13	6 ± 3	-	8	7	4	5	0	0	0
PSP	14	9	67 ± 12	7 ± 6	-	3	6	4	4	0	0	0
CBS	6	2	71 ± 4	5 ± 2	-	2	5	0	1	0	0	0
Unclassified	7	5	56 ± 14	10 ± 8	-	0	5	1	1	0	0	0
Total	160	95	55.68 ± 13	11.6 ± 7.8	43	37	81	42	30	1	1	3

STN DBS = subthalamic nucleus deep brain stimulation.

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presence of psychosis) that was generally poorly controlled with symptomatic drugs.

Fifty-eight percent of the patients with PD had more than 10 years of disease duration. A proportion of these individuals (43/117) had received prior deep brain stimulation (DBS).

The main indication for BTX treatment was pain (50.6% of cases). The two types of pain for which BTX was given were dystonic pain (77.6% of the cases) and musculoskeletal pain (22.4% of the cases). None of the two types of pain had shown response to adjustments in antiparkinsonian medications or DBS parameters or to treatment with analgesic drugs. For dystonic pain, the main locations were the lower limbs (63.5%), followed by upper limbs (11.1%), neck (11.1%), and paraspinal muscles (1.59%); however, in most cases (22%), painful dystonia was present in multiple locations Also for musculoskeletal pain, the lower limbs were the main location of pain (50%), followed by upper limbs (16.7%), neck and shoulders (11.1%), and multiple locations in the rest of the patients. In term of diagnosis, dystonic pain was the most frequent finding in PD, PSP, and unclassified parkinsonism (86%, 71.5%, and 100% respectively), and musculoskeletal pain was the most prevalent in patients with MSA and CBS (60% and 71.5%).

Functional impairment resulting from dystonia was the second most common indication, including blepharospasm, gait difficulties from foot dystonia, and oromandibular dystonia (26.25%) (Table 1). Other indications were the treatment of sialorrhea (18.75%), and camptocormia (1.25%). One patient with PD was treated for freezing of gait and three patients with PD were treated for tremor. The characteristics of the treatment including duration of the treatment, intervals between injections, and BTX dose range for each indication by diagnostic group, are summarized in Table 2. The average duration of BTX use was 29.23 months (range, 3-156 months).

The subjective CGI of BTX treatment outcomes are shown in Table 3. Considering pain as the indication, 81% of all patients with PD reported subjective benefits (score of + 1 or greater) after the first BTX injections, with 53.4% of the cases describing response as very much improved. This benefit was maintained after the last recorded BTX visit with no significant difference in outcome compared with the first injection; thus, 39.7% of subjects with PD still reported a very much-improved outcome ($p = 0.067$). Similar results were observed in patients with PSP, MSA, and CBS that received the BTX treatment for pain (Table 3). Logistic regression analysis showed that there were no differences in outcomes between patients with dystonic pain or musculoskeletal pain ($p = 0.39$), dose of BTX ($p = 0.153$, adjusted for location of pain), or diagnosis ($p = 0.375$).

In the 37 patients from the palliative care clinic, pain was the main indication for BTX, and the results showed a reduction of pain in 62.2% of the patients (data not shown). As expected from the known benefits of BTX for dystonia, functional disturbances resulting from dystonia resulted in improvement. The PD patient with freezing of gait reported subjective benefit after the first set of BTX but no response after the following injections. Only 11 of 117 patients reported local minor adverse effects related to the injections (Table 4). In those that reported adverse effects, the dose and pattern of injections was adjusted after the first visit and maintained during the rest of the treatment. Most of the patients continue receiving the treatment in our clinic (43.1%). Among the ones that discontinued the injections, the main reasons were DBS treatment and symptom improvement (7.5%), limitations for transfers to the clinic because of disease progression (9.4%), patient request to no longer receive injections (11.8%), absence of expected response (12.5%), and death (5.6%). There is no follow-up information for 10% of the patients.

Discussion

This review of our 20-year experience with BTX treatment in advanced parkinsonism shows that injections are a safe and useful tool for the treatment of many symptoms that are often challenging to treat. In particular, focal dystonic symptoms can be helped and drooling reduced with carefully targeting BTX injections.

The most interesting finding is that the main indication for the use of BTX in our clinic is pain. The cause of pain in this cohort was likely multifactorial and resulted from dystonia or musculoskeletal pain. Spasticity may also play a role in pain in some subjects with PSP/CBS subjects. Pain is a common and underdiagnosed non-motor symptom in parkinsonism and associated with reduced health-related quality of life.[19] In some patients, pain is so severe and intractable that it overshadows the motor symptoms of the disorder.[19] In 2008, a cross-sectional survey of 450 PD patients reported that two-thirds of the parkinsonian patients had chronic pain and in most cases was unreported and untreated.[20] Pain is often not recognized, even by experienced health care professionals, and it is estimated that pain remains undeclared in 40% of patients.[21] Treatment options for pain in this population

Table 2: BTX treatment characteristics

			BTX dose expressed in Units (range)					
	Duration of treatment (months) Mean (range)	Intervals between injections (months) Mean (range)	Pain	Functional disturbances from dystonia	Sialorrhea	Camptocormia	Freezing of gait	Tremor
PD	32 (3-156)	3 (3-6)	100-600	6-260	20-160	75-200	300	150
MSA	20 (3-60)	3 (3-4)	150-500	30-230	30-80	-	-	-
PSP	23 (3-72)	3 (3-4)	100-500	15-50	40-100	-	-	-
CBS	21 (3-48)	3	130-400	-	40	-	-	-
Unclassified	28 (3-120)	3	125-225	125	60	-	-	-
Total	29.23 (3-156)	3	100-600	6-260	20-160	75-200	300	150

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Table 3: Subjective Clinical Global Impression after the first and the last BTX injections

Diagnosis	Indication	Treatment duration in months	Response to the treatment with BTX (%) after the first injections					Response to the treatment with BTX (%) after the last injections					
		Mean (range)	Very much improved	Much improved	Minimally improved	No change	Worse	Very much improved	Much improved	Minimally improved	No change	Worse	p
PD	Pain	29 (3-156)	31 (53.4)	15 (25.9)	1 (1.7)	9 (15.5)	2 (3.5)	23 (39.7)	19 (32.8)	6 (10.3)	10 (17.2)	0	0.067
	Functional disturbances from dystonia	47 (3-156)	21 (61.8)	9 (26.5)	1 (2.9)	2 (5.9)	1 (2.9)	16 (47.1)	12 (35.3)	3 (8.8)	3 (8.8)	0	0.102
	Sialorrhea	21 (3-108)	7 (36.8)	7 (36.8)	1 (5.3)	4 (21.1)	0	2 (10.5)	6 (31.6)	5 (26.3)	6 (31.6)	0	0.025
	Camptocormia	15 (6-24)	1 (50)	0	0	1 (50)	0	1 (50)	0	0	1 (50)	0	-
	Freezing of gait	6	1 (100)	0	0	0	0	0	0	0	1 (100)	0	-
	Tremor	24 (3-36)	1 (3.3)	1 (3.3)	0	1 (3.3)	0	0	0	2 (6.7)	1 (3.3)	0	-
MSA	Pain	14 (3-24)	3 (42.8)	2 (28.6)	0	2 (28.6)	0	0	4 (57.1)	1 (14.3)	2 (28.6)	0	0.046
	Functional disturbances from dystonia	39 (24-60)	4 (100)	0	0	0	0	3 (75)	1 (25)	0	0	0	-
	Sialorrhea	3 (12-24)	1 (20)	1 (20)	1 (20)	1 (20)	1 (20)	1 (20)	1 (20)	2 (40)	1 (20)	0	0.655
PSP	Pain	24 (3-36)	2 (33.3)	2 (33.3)	0	1 (16.7)	1 (16.7)	0	4 (66.7)	0	2 (33.3)	0	0.564
	Functional disturbances from dystonia	16 (3-24)	2 (50)	1 (25)	0	1 (25)	0	0	3 (75)	0	1 (25)	0	'-
	Sialorrhea	29 (3-72)	1 (25)	1 (25)	1 (25)	1 (25)	0	1 (25)	1 (25)	0	2 (50)	0	-
CBS	Pain	24 (12-48)	5 (100)	0	0	0	0	2 (40)	3 (60)	0	0	0	0.083
	Sialorrhea	3	0	1 (100)	0	0	0	0	1 (100)	0	0	0	.-
Unclassified	Pain	36 (6-120)	4 (80)	0	0	1 (20)	0	3 (60)	1 (20)	0	1 (20)	0	0.317
	Functional disturbances due to dystonia	3	0	1 (100)	0	0	0	0	1 (100)	0	0	0	.-
	Sialorrhea	12	0	1 (100)	0	0	0	0	0	1 (100)	0	0	.

Table 4: Adverse effects

n	Indication	Adverse events
1	Blepharospasm	Blurred vision
1	Blepharospasm	Tearing
1	Sialorrhea	Dry mouth
2	Blepharospasm	Ptosis
2	Sialorrhea	Dysphagia
4	Pain	Transient weakness

remain generally poor because of either lack of benefit or tolerability issues. Often, dystonic or musculoskeletal pain does not respond to levodopa or dopamine agonist. Surgical treatments have been suggested including subthalamic nucleus or internal globus pallidus DBS, with variable benefit.[22,23] In a recent review about emerging analgesic treatments for PD, a range of options is suggested, including duloxetine and cranial electrotherapy stimulation.[24] Clinical trials in PD subjects with pain using repetitive transcranial magnetic stimulation or oxycodone/naloxone prolonged-release tablets are under way. Unfortunately, many of the current treatments for pain can worsen other common symptoms such as constipation, hallucinations, and confusion, and most of the patients in later stages of the disease are not candidates for surgical treatment.

We acknowledge that the retrospective, open label design of the study and the use of a subjective CGI are the main limitations of this study. However, the unequivocal responses in the CGI scale and the ongoing patient and caregiver request for BTX supports the benefit these patients experienced. Currently, pain in PD is an off-label indication for BTX treatment in Canada and therefore lacks financial coverage. In our clinic, patients are grouped into those that were granted provincial authorization after showing the results of the injections and the lack of alternatives, those that received compassionate provision of the drug, and those that paid out of pocket for the cost of the treatment. Adding evidence for the usefulness of BTX in pain and other symptoms in PD may conduce insurance companies to consider covering the use of BTX for these indications. Further discussion about the cost implications of the treatment is beyond the scope of this article.

Our results suggest that BTX could be safely used in patients with parkinsonism, including patients in advanced stages of the disease. Only 11 adverse effects were reported, none of which was serious and all were transient. Most patients reported benefit with reduction of the pain; in particular, these results are relevant for patients with very advanced disease in whom severe adverse effects are more likely to occur with the use of other treatments for pain.

Conclusion

Our retrospective results confirm the safety and efficacy of different uses of BTX in the symptomatic treatment of patients with parkinsonism even in advanced stages of the disease, and suggest BTX treatment could have a safe and useful role in the treatment of pain when it has no response to standard analgesics.

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