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Evaluation of atrophy after botulinum toxin injection in cervical dystonia by MRI

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Abstract

Objectives: Cervical dystonia (CD) is one of the most common forms of dystonia seen clinically, Botulinum neurotoxin type A (BoNT) is known as the first-line therapy for CD. One of the most critical side effects of chronic exposure to BoNT is developing muscle atrophy which causes cosmetic issues and future injection difficulty. In this study, we examined the degree of atrophy caused by botulinum toxin injection, as the most effective treatment of CD, and the factors affecting it to reduce atrophy. *Methods:* Patients underwent treatment by injecting standard doses of BoNT for 12 months. Soft-tissue cervical MRI was performed for seven patients before treatment and 12 months later. Sternocleidomastoid and splenius capitis in the transverse cut in T1 MRI view were measured in MRIs for each patient, and muscle atrophy volume was calculated. *Results:* Two patients were male, five were female, and the mean age was 40 ± 12.76 years. The amount of atrophy increased significantly with increasing injection dose and frequency. Muscular atrophy was significantly higher in people older than 50 years, but gender and body mass index (BMI) had no significant effect.
Conclusion: Muscular atrophy is more likely in older patients, those treated with higher doses of BoNT, and those who received more frequent injections.

Keywords: Cervical dystonia, MRI, muscle atrophy, botulinum toxin

INTRODUCTION

Dystonia is a chronic disorder characterized by continuous or intermittent involuntary muscle contraction, causing repetitive and twisting movements or abnormal posture.[1,2] Dystonia is the third most common movement disorder after Parkinson's disease and essential tremor.[3] Cervical dystonia (CD) is the most common form of focal dystonia involving the muscles of the neck and sometimes the shoulders.[4] Disability, functional and social disorders, in addition to neck and shoulder pain, are the most critical debilitating features of this disease.[5] The estimated prevalence rate of CD in Europe is 5,7/100000, and in the USA is around 8,9/100000.[6] It is also more common in women.[7]

Most CD cases are idiopathic, and approximately 12% are associated with a hereditary component.[8] CD can also be secondary to certain medications, excessive toxin production into the body, or structural lesions caused by trauma or vascular insults.[9]

Several categories of drugs (anticholinergic, antidopaminergic, dopaminergic, gabaergic) are reported to be effective in CD patients based on uncontrolled studies.[10] Today we use Botulinum toxin type A (BoNT) as the first-line therapy for CD; as there is no definitive medical treatment for cervical dystonia.[11-14]

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A systemic study shows that botulinum toxin injection's most common side effects in CD treatment include dysphagia, ptosis, cervical muscle weakness, and dry mouth.[10] Chronic exposure to BoNT also causes muscle atrophy which can cause cosmetic issues and future injections difficulty due to decreased muscle volume.[15] However, there is little data about BoNT injection-induced muscle atrophy and the factors affecting it.[15] There is a study by Durand and his colleagues about muscle atrophy caused by botulinum toxin injection for cosmetic purposes. There needs to be more data about the degree of atrophy, classification, and precise mechanism of atrophy.[16]

MRI is effective in assessing muscle diseases like myxoedema and muscle atrophy, and we can determine different patterns and degrees of atrophy and fatty infiltration in muscle using imaging techniques.[17] In a study, Brogna and colleagues also used muscle MRI to assess involvement patterns and the degree of muscle atrophy in MSA patients.[18] So, in this study, for the first time, we study the degree of atrophy caused by botulinum toxin injection and the factors affecting this atrophy.

METHODS

All subjects were recruited for the study from the Movement Disorders clinic of Shohada-e-Tajrish university hospital from 2018 to 2021. Patients meeting the following inclusion criteria were eligible for this study: 1) ≥ 18 years of age, 2) diagnosed with idiopathic cervical dystonia by a Movement Disorders specialist, 3) Naïve to botulinum toxin A.

Patients were excluded if they had: 1) Any neurological disorder such as amyotrophic lateral sclerosis and motor neuropathy, Lambert-Eaton syndrome, and myasthenia gravis, which increase risk in patients after exposure to Botulinum Toxin Type A, 2) Muscle weakness or paralysis, mainly in the treatment area, 3) active infections or skin diseases at the treatment area, Patients underwent treatment by injecting a standard dose of abobotulinumtoxinA (Dysport®) prescribed by the neurologist every three months for 12 months. Demographic and clinical characteristics, injected muscles, and dosage of injections in each muscle were recorded for each patient.

MRI acquisition

Soft-tissue cervical MRI was performed for all the patients before treatment and 12 months.

Axial and sagittal MRI of cervical muscles were acquired on a 1.5 Tesla magnetic resonance scanner (Tim Trio [Nijmegen] or Magnetom Verio [Paris]; Siemens, Erlangen, Germany) using a phased-array spine coil in combination with the surface coil.

T1-weighted spin-echo sequence and three-dimensional chemical shift–encoded Dixon sequences were applied for semiquantitative and quantitative assessment of fat infiltration and muscle CSA. Tissue water distribution and edema were assessed semi-quantitatively with a turbo inversion recovery magnitude (TIRM) sequence and quantitatively with a multi-echo spinecho sequence (T2water). A baseline MRI was performed within one month after the first trial visit (before treatment was started), and a follow-up MRI was performed after 12 months.

Injected muscles areas in the transverse cut in T1 MRI view were measured three times on different days with tools available in "pacs manager 2020" software, in both performed MRIs (before and after treatment with botulinum toxin). And repeated data was considered as muscle area.

Because of the low number of samples in some muscles or the low quality of MRI in some patients, the muscles were limited to sternocleidomastoid (SCM) and splenius capitis. A total of eighteen muscles were examined and measured.

We measured SCM muscles in the True cord transverse cut, and splenius capitis muscles were measured in the C5 cut. Atrophy volume for muscles was measured using the following formula:

$$\frac{primary\ area - secondary\ area}{primary\ area} * 100$$

Data analysis method

The data were analyzed by mean, standard deviation, median, amplitude, frequency, and percentage. Inference statical tests were used to compare variables before and after botulinum toxin treatment. All analyzes were performed by 'SPSS 25' statical software. A P-value less than 0.05 was considered statistically significant.

RESULT

In the study, twenty-five patients were recruited; due to the onset of the COVID-19 pandemic, some patients were lost to follow-up, and finally, seven patients completed the study. All 25 patients did the first MRI, but the second was performed for seven patients. The study was conducted on two

men (28.6%) and five women (71.4%). The mean age of participants was 40 ± 12.76 years in the 22-57 years old domain.

We compared the cross-sectional area obtained by the first and the second MRIs with the Wilcoxon test. There was a statistically significant difference between the first and second MRI (p value=0.028). MRI evaluation of muscle size is shown in Figure 1.

The results have been classified into four main groups according to the injection frequency (Group1-twice, Group2-three times, Group3-four times, and Group4-five times). One-way ANOVA analysis has been performed, as shown in Figure 2, and the difference in the results of the four groups was significant (p=0.001 F=13.0). As the Tamhane test demonstrated, the mean of atrophy in the fourth group (22.13±3.17) was significantly higher than the second (5.6±2.3 p=0.00) and the third group (10.55±2.75 p=0.002).

Considering the age of patients, all of the study patients were classified into three-main domains: (domain 1: 20-30 years old, domain 2: 40-50 years old, domain 3: 50-60 years old), and atrophy percentage data were assessed and analyzed via One-way ANOVA which has shown a significant difference. Due to the Least Significant Difference (LSD) test, which was applied , the results have shown a significantly higher atrophy percentage in the third group (20.92±5.48) than in the first (12.88±7.24 p=0.035) and the second group (6.58±4.26 p=0.001) but no such difference between the first and second groups (p=0.075).

There was a negative relationship between muscular atrophy and Body Mass Index (BMI), which was not statistically significant.

DISCUSSION

This study which included seven patients from February 2019 to September 2021, demonstrates that the dosage of botulinum toxin injections and the frequency of administrations are related to the degree of atrophy. The atrophy is also significantly higher in ages over 50 years. There is no significant difference between men and women in the degree of atrophy. We examined SCM and splenius capitis muscles; however, our data do not show a significant difference in degree of atrophy between these two muscles. In this

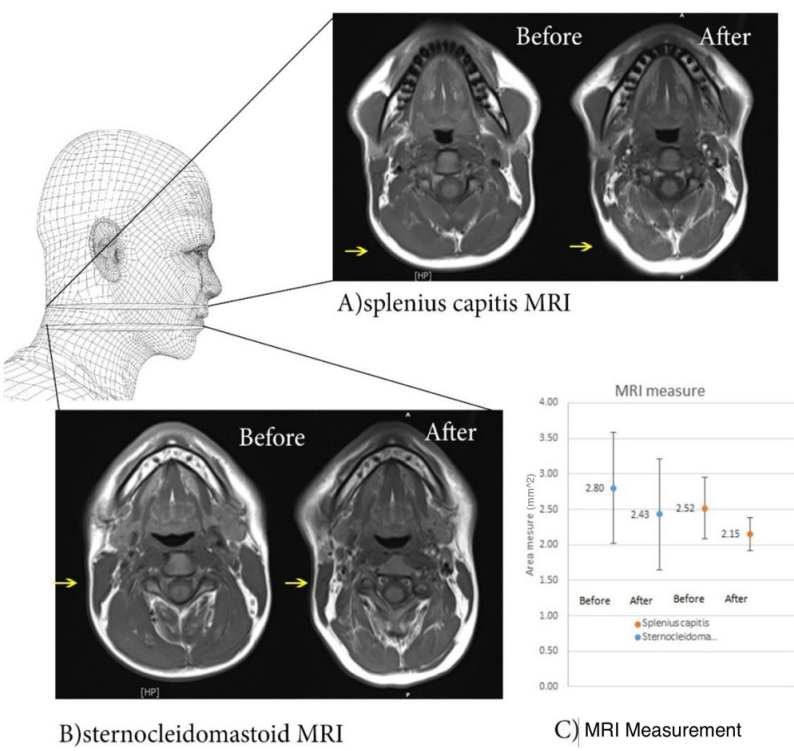

Figure 1. MRI evaluation of muscle size. This figure compares The size of splenius capitis (A) and Sternocleidomastoid (B) before and after BoNT administration as observed via MRI imaging. The muscle area in the MRI section was measured and compared (C).

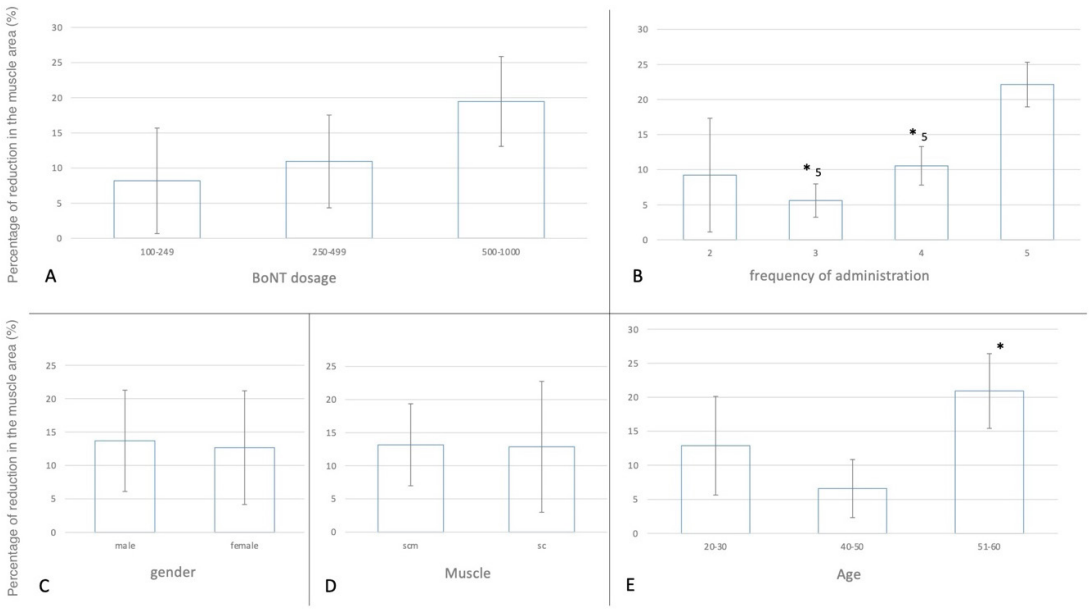

Figure 2. BoNT atrophy contributing factors. Comparing the different contributing factors' effects on the magnitude of BoNT-induced atrophy resulted in finding a significant effect of BoNT dosage (A), frequency of administration (B), and age (E). Gender (C) and the muscle type (D) were not significantly effective.

study, three patients were overweight, others in the normal range, and none were obese, and there was no significant association between atrophy and BMI. BoNT atrophy contributing factors are demonstrated in Figure 2.

Durand and his colleagues' also mentioned that the botulinum injection's therapeutic effects and atrophy size are related to the dosage and interval between each injection.[16] Fortuna also measured muscle mass changes in rabbits after repetitive injections administered at monthly intervals, and approximately 60% muscle mass loss was noted after three months.[19] In another study, Koerte measured procerus muscle atrophy after a single dose of onabotulinum-toxin A. After a month, a 46% - 48% reduction in size was observed that lasted for one year.[20] After injection, the average atrophy in our patients was 13% which showed less degree of atrophy. The measuring method in this study was similar, and muscle cross-section was used for measurement. Nevertheless, these studies did not address the factors contributing to atrophy.

The dosing and frequency of injections play a crucial role in the extent of atrophy. Salari *et al*. have reviewed the underlying mechanisms. These suspected mechanisms include; preventing muscle re-innervation, skeletal muscle fiber type composition, the capacity of the satellite cells of the injected muscle, mitochondrial dysfunction, number of muscle spindles, muscle blood perfusion, and fat deposition. Considering these mechanisms may impact the dosing and frequency of injections to reduce the side effects.[15]

Skeletal muscle has three types of fibers: type I, IIa, and IIb. Type I fibers tend to develop and re-innervate faster compared to type IIb fibers after BoNT-induced atrophy. Therefore, muscles abundant in type I fibers recover better and faster. The fiber type composition of different muscles varies depending upon their location and function in the body and varies in different people. As a result of this difference in fiber type composition, injection of BoNTs will produce a differential amount of atrophy.[21-24] As mentioned above, muscle fibers type IIb are more sensitive to atrophy, and also with increasing age, the ability of type IIb fibers regeneration decreases more than ever.[22,25,26] These considerations may explain the high rate of atrophy over 50 years. It has been said that some androgen receptors on men's skeletal muscles make muscle fibers differentiate into type I. As mentioned, type I fibers have more ability to regenerate and, therefore, more resistant to atrophy.[27] Salari mentioned in their review that SCM muscles have more IIb fibers than splenius capitis. As a result, SCM muscle is expected to be more sensitive to atrophy due to botulinum toxin.[15] Another study has shown that obesity relates to decreasing muscle fibers type I and causes more

atrophy.[15,28] However, our study does not support these explanation. This may be due to the limited number of patients in this study.

So far, few studies have quantified muscle atrophy caused by botulinum toxin injection, but none have examined the factors affecting BoNT-induced atrophy. The strengths of this study include the novelty of this research and the assessment of different factors that can affect atrophy by botulinum toxin injection. The limitations are firstly, the few number of cases in this study, as CD is a rare disorder. This is also duet to the COVID-19 pandemic, which caused patients to be lost to follow-up. Low-quality MRI pictures and lack of similar muscle pictures in some patients are other limitation of this study.

In conclusion, repeated botulinum toxin injection can result in a decrease in muscle volume, and the dosage of botulinum toxin injections and the frequency of administrations in older patients increases the atrophy size. There has been no correlation between atrophy and gender, muscle type, or BMI.

DISCLOSURE

Ethics: The study was approved by the local ethics committee of Shahid Beheshti University of Medical science (IR.SBMU.RETECH.REC.1399.258). Written informed consent was obtained from all subjects.

Data availability: Data is available upon request from the corresponding author.

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Conflict of interest: None

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