Intramuscular Pressure Before and After Botulinum Toxin in Chronic Exertional Compartment Syndrome of the Leg: A Preliminary Study
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What is This?
**Intramuscular Pressure Before and After Botulinum Toxin in Chronic Exertional Compartment Syndrome of the Leg**

**A Preliminary Study**

Marie-Eve Isner-Horobeti,§ MD, PhD, Stéphane Pascal Dufour,§ PhD, Cyril Blaes,† MD, and Jehan Lecocq,§ MD

*Investigation performed at Strasbourg University, Department of Physical Medicine and Rehabilitation, Strasbourg, France*

**Background:** Botulinum toxin A (BoNT-A) is used in the treatment of muscle hypertrophy but has never been used in chronic exertional compartment syndrome (CECS). The objective diagnostic criterion in this condition is an abnormally elevated intramuscular pressure (IMP) in the compartment. In this study, the IMP was measured 1 minute (P1) and 5 minutes (P5) after the exercise was stopped before and after BoNT-A injection.

**Hypothesis:** Botulinum toxin A reduces the IMP (P1 and P5) and eliminates the pain associated with CECS.

**Study Design:** Case series; Level of evidence, 4.

**Methods:** Botulinum toxin A was injected into the muscles of moderately trained patients with an anterior or anterolateral exertional compartment syndrome of the leg. The BoNT-A dose (mean ± SD) ranged from 76 ± 7 to 108 ± 10 U per muscle, depending on which of the 5 muscles in the 2 compartments were injected. The primary end point was IMP (P1, P5). Secondary end points were exertional pain, muscle strength, and safety. Follow-up was conducted up to 9 months.

**Results:** A total of 25 anterior compartments and 17 lateral compartments were injected in 16 patients. The time interval (mean ± SD) between the BoNT-A injection and after BoNT-A injection IMP measurement was 4.4 ± 1.6 months (range, 3-9 months). In the anterior compartment, P1 and P5 fell by 63% ± 17% (P < .00001) and 59% ± 24% (P < .0001), respectively; in the lateral compartment, P1 and P5 fell by 68% ± 21% (P < .001) and 63% ± 21% (P < .01), respectively. Exertional pain and muscle strength were monitored, based on the Medical Research Council score. The exertional pain was completely eliminated in 15 patients (94%). In 5 patients (31%), the strength of the injected muscles remained normal. In 11 patients (69%), strength decreased from 4.5 (out of 5) to 3.5 (P < .01), although without functional consequences. In the conditions of this study, BoNT-A showed a good safety profile in patients with CECS.

**Conclusion:** In this case series, BoNT-A reduced the IMP and eliminated exertional pain in anterior or anterolateral CECS of the leg for up to 9 months after the intervention. The mode of action of BoNT-A is still unclear. A randomized controlled study should be carried out to determine whether BoNT-A can be used as a medical alternative to surgical treatment.

**Keywords:** exertional compartment syndrome; botulinum toxin; leg pain; intramuscular pressure

A muscle compartment is a closed space bound by fascia and bone. The leg includes 4 compartments: the anterior compartment, the lateral compartment, the superficial posterior compartment, and the deep posterior compartment. Chronic exertional compartment syndrome (CECS) is characterized by 2 criteria. The first one is a subjective clinical criterion: pain in the involved compartment triggered by a specific exercise and disappearing when the exercise is stopped. The second one is a paraclinical criterion and the only objective diagnostic criterion: an abnormally high intramuscular pressure (IMP) after exercise within the affected compartment. The pathophysiological process of CECS is poorly understood and probably multifactorial. One of the hypotheses is a discrepancy between the tissue delimiting the compartment and its muscle content, resulting in an excessive IMP. This discrepancy may be due to a hypertrophy of the muscles within the compartment. However, other plausible pathophysiological mechanisms are also suggested for CECS, including a decreased compartment syndrome size due to a thickened, unelastic fascia, a supernumerary muscle, or a vascular anatomic or functional abnormality. The pain could be explained by...
diagnosis of CECS, that is, the IMP and associated pain. The only curative treatment available for CECS, and considered the gold standard, is a surgical fasciotomy or fasciectomy to release the tension on the compartment’s boundary. However, the postoperative recurrence rate varies from around 3% to 17% and may reach 35% in partial fasciectomy. Therefore, a less invasive alternative may be of interest.

Given the proposed role of muscle hypertrophy within the compartment, botulinum toxin A (BoNT-A) could help in the management of CECS by reducing the volume of the compartment content. BoNT-A showed favorable and promising results in the treatment of masseter hypertrophy and gastrocnemius hypertrophy. Likewise, its use for analgesic purposes in painful hypertrophy of the calf muscles and painful muscle contractures associated with myofascial syndromes has been described. The similarity between the symptoms of these conditions led us to examine the effects of BoNT-A in CECS.

Although any muscle compartment can be affected, CECS most commonly involves the anterior and lateral compartments of the leg. These 2 compartments are subcutaneous and are more readily accessible and safe for exploration. Consequently, our study focused on CECS involving the anterior and anterolateral compartments of the leg. A first case series conducted in 2008 in 7 patients with anterior or anterolateral CECS of the leg showed that BoNT-A injections helped reduce muscle pain in the affected compartments. However, the effects of BoNT-A on IMP have never been investigated in CECS. Therefore, we hypothesized that intramuscular injections of BoNT-A may reduce IMP and relieve pain. Our objective was to test the effect of BoNT-A injection on the only objective criteria able to confirm the diagnosis of CECS, that is, the IMP and associated pain.

MATERIALS AND METHODS

Population

Clinical files from a population of patients seen between January 2010 and June 2012 at a physical and rehabilitation medicine department were retrospectively analyzed. During this period, 148 patients were seen in consultation for leg pain. We retained complete clinical and paraclinical data in patients’ files according to 3 criteria. First, CECS had to be suggested clinically in the anterior or anterolateral compartment by the presence of leg pain, triggered by physical or sport activity, irrespective of the patients’ age or sex. Second, patients had to be injected by BoNT-A in the involved compartment. These patients had to be BoNT-A naïve and to have given their written consent to receive the proposed intramuscular injection. The third criterion was the assessment of IMP before and after BoNT-A injection.

In these patients, the CECS could be unilateral or bilateral. The definitive diagnosis was based on an elevated IMP measured in the involved compartments after running, based on the criteria suggested by Pedowitz et al: IMP at the first minute after exercise (P1) greater than 30 mm Hg and/or IMP at the fifth minute (P5) greater than 20 mm Hg. Other excessive leg pain causes were ruled out by a clinical examination (general, orthopaedic, neurological, and functional) and paraclinical examination (full blood examination, leg radiographs, bone scintigraphy, lumbar scan, and dynamic echo-Doppler of the lower limbs). Those with abnormal findings in the above-mentioned examinations (periostitis, stress fracture, herniated disk, vascular compression) were excluded from the analysis.

Using these inclusion criteria, we identified 16 patients, consisting of 11 recreational runners and 5 military runners. These runners had all been running regularly for more than 1 year and had a training volume of at least 5 hours per week. Patients had undergone treatment (eg, rest, stretching, ice, nonsteroidal anti-inflammatory drugs, analgesics) that proved unsuccessful for their persistent muscle leg pain and forced them to reduce or stop their usual physical activity. All members of this group were examined by the same physician. The following data were collected: age, sex, weight, height, body mass index, and time to diagnosis (Table 1).

<table>
<thead>
<tr>
<th>TABLE 1 Population Characteristics (N = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Sex, male/female, No.</td>
</tr>
<tr>
<td>Height, cm</td>
</tr>
<tr>
<td>Weight, kg</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>Time to diagnosis, mo</td>
</tr>
<tr>
<td>Anterior compartment</td>
</tr>
<tr>
<td>Anterolateral compartment</td>
</tr>
<tr>
<td>Unilateral involvement</td>
</tr>
<tr>
<td>Bilateral involvement</td>
</tr>
</tbody>
</table>

*Data given as mean ± standard deviation (range) unless otherwise noted.

Evaluation and Follow-up

Clinical data and IMP were obtained just after the initial running test and before BoNT-A injection. After BoNT-A injection, IMP measurement was assessed only once after ~4.4 ± 1.6 months (range, 3-9

The authors declared that they have no conflicts of interest in the authorship and publication of this contribution.
Figure 1. Study design: All patients had chronic exertional compartment syndrome (CECS) for a mean (±SD) duration of 40 ± 60 months before the first visit to the medical department. During this time, all other exertional leg pain causes were discarded. At the first visit, all patients were asked to run on a treadmill to demonstrate the effects of the usual pain in their lower leg muscles. Intramuscular pressure (IMP) was measured 1 and 5 minutes after running to confirm CECS, and lower leg muscle strength and pain were evaluated. The intramuscular botulinum toxin A (BoNT-A) injection was given 15 minutes after the running test. Patients returned to the department after 1 month of recovery from the BoNT-A injection for evaluation of lower leg muscle strength, pain, and side effects. All patients had their last visit between 3 and 9 months after BoNT-A injection; at this visit, the running test was repeated, IMP was measured, and lower leg muscle strength, pain, and side effects were evaluated.

Running Test

To trigger their usual leg pain, all patients performed a treadmill running test (Medical Development S2500, Andrezieux Boutheon, France) before and 4.4 ± 1.6 months after BoNT-A injection. The running speed was increased progressively until the patient complained of leg pain. The exercise was then stopped and the patient was placed supine for immediate IMP measurements. The running protocol after BoNT-A injection was identical to the protocol used before the injection. Thus, each patient was asked to run at the same speed and for the same duration in both tests.

Special Procedures and Measurements

**IMP in the Lower Leg Compartments.** Before the exercise test, local skin anesthesia was given (1.5 mL, 1% xylacaine) at the point where the IMP needle would be inserted. The needle, connected to a pressure transducer (Stryker Instruments, Mahwah, New Jersey), was inserted immediately into the anterior or lateral compartment. The pressures in the compartment and in the transducer were evened out by use of a syringe filled with 0.2 mL of saline solution. The pressure was displayed on the transducer in mm Hg and was read about 10 seconds after saline injection, as previously described in clinical settings. The IMP was measured continuously, but we recorded only the values at 1 minute (P1) and 5 minutes (P5) after the exercise. After BoNT-A injection, the IMP was measured in the same conditions and with the same procedures as used for the initial measurements.

**Clinical Data.** Clinical data (ie, exertional pain, muscle strength, and safety) were obtained before as well as 1 month and 4.4 ± 1.6 months (range, 3-9 months) after the injection of BoNT-A.

**Exertional Pain.** Pain was assessed as binary data (ie, present or absent) irrespective of its intensity, and therefore a quantified visual analog scale was not necessary. The analgesic effect of BoNT-A was thus considered as positive only if the pain had disappeared after the injection of BoNT-A.

**Muscle Strength.** Muscular strength was assessed with the semiquantitative Medical Research Council score (0 to 5). To aid statistical calculations, intermediate values typically represented with the plus (+) symbol were replaced by the decimal 0.5. The duration of muscular strength loss was quantified in months. The functional consequences of any muscle impairment were evaluated during the interview as a feeling of ankle instability when walking or running, as well as the ability to walk on heels.

**Safety.** The potential side effects of BoNT-A (general muscle weakness, muscular atrophy, flulike symptoms, breathing and swallowing difficulties, and death) were exhaustively explained to study participants before they gave their written consent to receive the proposed intramuscular injection. After the injection, all patients were given the option to call the examiners at any time during the follow-up for any concerns, including occurrence of a potential side effect.

**Intramuscular Injection of BoNT-A.** At 15 minutes after the initial running test, the BoNT-A injection was performed under electrical stimulation guidance, which was used to position the needle as close as possible to the motor endplate of all the muscles in the involved compartment.
and to avoid injecting a muscle more than once (Figure 2). To identify the injection site, a needle electrode 0.46 mm in diameter and 50 mm long (Bioject, Alpine Biomed Aps, Skovlunde, Denmark) was connected to a muscle electrical stimulation device (Cefar Rehab, Mouguerre, France) to detect the point that produced a maximum contraction with the minimum stimulation intensity for each muscle in the compartment.

In patients with an anterior CECS, BoNT-A was injected into each of the 3 muscles in the anterior compartment (tibialis anterior, extensor hallucis longus, extensor digitorum longus). In patients with an anterolateral CECS, BoNT-A was injected into the 3 muscles mentioned above and into the 2 muscles of the lateral compartment (peroneus brevis and peroneus longus).

The BoNT-A (Dysport, Ipsen, Boulogne-Billancourt, France) was reconstituted with 2.5 mL of saline solution for 500 U. Because of the lack of previous studies, the selection of the dose of BoNT-A was based on the literature and on the authors’ experience and knowledge of spasticity7,40 and musculoskeletal disorders.41,49,54 The objective was to use the minimum effective dose that would not lead to muscle paralysis. This dose was one-third of the maximum recommended dose used for the treatment of lower limb spasticity,7,40 adjusted to the volume of the muscle and the patient’s body weight. BoNT-A was injected into each muscle in a single injection site.

The doses of BoNT-A administered in each muscle (measured in units) as well as the dose per muscle based on the patient’s body weight (units per kilogram) were recorded. The total dose of BoNT-A injected into each compartment was also recorded in units and units per kilogram (Table 2).

### Table 2

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Anterior Compartment</th>
<th>Lateral Compartment</th>
</tr>
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<td>16</td>
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### Table 3

<table>
<thead>
<tr>
<th>Intramuscular Injection of Botulinum Toxin A in 42 Compartments</th>
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<tbody>
<tr>
<td>Patient No.</td>
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<tr>
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<tr>
<td></td>
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<td>16</td>
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### Results

#### Effect of BoNT-A Injection on Intramuscular Pressure

The IMP was measured before and after the intramuscular injection of BoNT-A in 42 compartments (25 anterior and 17 anterolateral compartments in 16 patients). Of note, some patients presented mono/bilateral and/or anterior/anteralateral CECS (Tables 1 and 3).

The mean interval between BoNT-A injection and post-injection IMP measurement was 4.4 ± 1.6 months (range, 3-9 months).

The Student t test was used to compare the parameters before and after BoNT-A.

The results were expressed in terms of mean, standard deviation, and range. The significance level was P < .05. Correlation tests were based on the Pearson correlation coefficient.

#### Statistical Analysis

To specifically test the effects of BoNT-A injection on the anterior or anterolateral compartments, IMP values were assessed per muscle compartment. For clinical data (ie, pain and muscle strength), the statistical analysis was performed per patient.

The Student t test was used to compare the parameters before and after BoNT-A.

The Student t test was used to compare the parameters before and after BoNT-A.
asymptomatic, but IMP values remained high (P1 = 35 mm Hg, P5 = 24 mm Hg). Of note, preinjection values were high (P1 = 75 mm Hg, P5 = 62 mm Hg). For the second patient, postinjection IMP values remained high (P1 = 46 mm Hg, P5 = 21 mm Hg) and pain persisted. This patient was directed to successful fasciotomy.

After the BoNT-A injection, in the lateral compartment, P1 and P5 decreased by 68% ± 21% (P < .001) and 63% ± 21% (P < .01), respectively (Figure 4). Specifically, P1 dropped to ≤30 mm Hg and P5 to ≤20 mm Hg in 15 patients, whereas they remained greater than normal in 1 patient, in whom P1 was 34 mm Hg (vs 57 mm Hg before BoNT-A injection) and P5 was normalized (10 mm Hg vs 36 mm Hg before BoNT-A injection). This patient became asymptomatic.

The extent of the reductions in P1 and P5 in the anterior and lateral compartments was similar. No correlation was found between the reduction in IMP in the anterior and/or lateral compartment and the total dose of BoNT-A injected into the compartment (Table 4).

**Effect of BoNT-A Injection on Clinical Data**

Clinical data were evaluated after 1 month and between 3 to 9 months (mean ± SD, 4.4 ± 1.6 months).

**Exertional Pain.** The exertional pain disappeared completely during the follow-up period in 15 patients (94%). The pain disappeared in less than 1 month in 10 patients (67%), in 1 to 3 months in 2 patients (13%), and in 3 to 5 months in 3 patients (20%). The 15 patients without pain after BoNT-A injection could exercise more at follow-up as they did not report any pain. Only 1 patient reported no pain reduction. This patient had persistently high IMP values after injection (cf IMP results) despite receiving a similar dose of BoNT-A (total dose of 300 U: 110 U in tibialis anterior, 110 U in extensor digitorum longus, and 80 U in extensor hallucis longus). At 5 months, a fasciotomy was recommended, and the patient completely recovered.

**Muscle Strength.** Muscle strength was rated as normal (5 on a scale from 0 to 5) for all muscles before BoNT-A injection.

The strength values per muscle 1 month after BoNT-A injection produced the following results: The mean (±SD) strength of the tibialis anterior was 4.6 ± 0.4 (4-5, P = .001) (values were normal [5/5] in 5 patients [31%], 4.5 in 8 patients [50%], and 4 in 3 patients [19%]). The mean strength of the extensor digitorum longus was 4.7 ± 0.4 (4-5, P = .001) (normal in 9 patients [56%], 4.5 in 5 patients [31%], and 4 in 2 patients [13%]). The mean strength of the extensor hallucis longus was 4.5 ± 0.6 (3.5-5, P = .001) (normal in 8 patients [50%], 4.5 in 3 patients [19%], 4 in 3 patients [19%], and 3.5 in 2 patients [12%]). The mean strength of the peroneus longus was 4.9 ± 0.3 (4-5, P = .19) (normal in 10 patients [84%], 4.5 in 1 patient [8%], and 4 in 1 patient [8%]); and the mean strength of the peroneus brevis was 4.9 ± 0.3 (4-5, P = .19) (normal in 10 patients [84%], 4.5 in 1 patient [8%], and 4 in 1 patient [8%]). Muscle strength rated normal for all muscles at 4.4 ± 1.6 months after BoNT-A injection.

The evaluation per study subject provided the following results: The strength of all muscles was normal (5/5) in 5 patients (31%), whereas it was reduced in 11 patients (69%). In these 11 individuals, the average muscle strength 1 month after BoNT-A injection was 4.5 in 6 patients and 4 in 5 patients without functional consequences. No correlation was found between the evaluation of strength of each of the 5 muscles and the dose of BoNT-A injected per muscle expressed in units or in units per kilogram of body weight (Table 5).

**Safety.** In 15 patients, no adverse effects were observed. Only 1 patient reported pain in the posterior compartment of her legs that was different from the anterolateral pain described previously. For this individual, BoNT-A was injected into the 3 muscles of the anterior compartment (total dose of 250 U: 90 U in tibialis anterior, 90 U in extensor digitorum longus, and 70 U in extensor hallucis longus). The BoNT-A dose was similar to the one used for the other 15 patients; the mean value was 288 ± 25 U. The IMP measured in the right deep posterior compartment and the muscle strength were both normal. There was no evidence suggesting that the pain reported might have been caused by the BoNT-A injection.
Correlation Between the Reduction in IMP and Doses of BoNT-A

<table>
<thead>
<tr>
<th>BoNT-A, U</th>
<th>P1, Anterior Compartment</th>
<th>P5, Anterior Compartment</th>
<th>P1, Lateral Compartment</th>
<th>P5, Lateral Compartment</th>
</tr>
</thead>
<tbody>
<tr>
<td>r = 0.12</td>
<td>r = 0.17</td>
<td>r = 0.24</td>
<td>r = 0.43</td>
<td></td>
</tr>
<tr>
<td>(P = .61)</td>
<td>(P = .46)</td>
<td>(P = .24)</td>
<td>(P = .43)</td>
<td></td>
</tr>
<tr>
<td>BoNT-A, U/kg</td>
<td>r = –0.37</td>
<td>r = –0.23</td>
<td>r = –0.35</td>
<td>r = –0.01</td>
</tr>
<tr>
<td>(P = .11)</td>
<td>(P = .33)</td>
<td>(P = .39)</td>
<td>(P = .99)</td>
<td></td>
</tr>
</tbody>
</table>

*BoNT-A, botulinum toxin A; IMP, intramuscular pressure; P1, IMP at 1 minute after cessation of exercise. P5, IMP at 5 minutes after cessation of exercise.

TABLE 5
Correlation Between the Tested Muscle Strength and Dose of BoNT-A

<table>
<thead>
<tr>
<th>Tibialis Anterior</th>
<th>Extensor Digitorum Longus</th>
<th>Extensor Hallucis Longus</th>
<th>Peroneus Brevis</th>
<th>Peroneus Longus</th>
</tr>
</thead>
<tbody>
<tr>
<td>BoNT-A, U</td>
<td>r = 0.21</td>
<td>r = 0.12</td>
<td>r = –0.25</td>
<td>r = –0.18</td>
</tr>
<tr>
<td>(P = .43)</td>
<td>(P = .636)</td>
<td>(P = .33)</td>
<td>(P = .55)</td>
<td>(P = .45)</td>
</tr>
<tr>
<td>BoNT-A, U/kg</td>
<td>r = –0.01</td>
<td>r = 0.25</td>
<td>r = 0.22</td>
<td>r = –0.22</td>
</tr>
<tr>
<td>(P = .97)</td>
<td>(P = .33)</td>
<td>(P = .39)</td>
<td>(P = .47)</td>
<td>(P = .60)</td>
</tr>
</tbody>
</table>

*BoNT-A, botulinum toxin A.

Moreover, after BoNT-A injection the patients did not complain about ankle instability during walking or running, and all were able to walk on their heels without pain.

**DISCUSSION**

The results of this case series show that an intramuscular injection of BoNT-A reduces intramuscular pressure in the compartments involved and eliminates exertional pain. These findings support our initial results in 2008 in a series of 7 patients who reported pain reduction after a BoNT-A injection in the muscles of the compartments affected by a CECS. This new case series is the first to examine the effects of BoNT-A on IMP, muscle pain, and muscle strength score in CECS patients.

**Effect of Intramuscular BoNT-A Injection on Intramuscular Pressure**

Our sample is representative of the population with CECS, as its characteristics are similar to those of other studies on anterior or anterolateral CECS of the leg. The patients’ average age was 23 years, and there was a marked male predominance (13 of 16 patients). The CECS was bilateral in almost two-thirds of the cases. The time to diagnosis, an average of 40 months, was close to that reported by Turnipseed et al. 69% lower than the preinjection values, with a significance level of .01 to .00001 depending on the compartment. The IMP values returned to normal in the majority of patients (87.5%, n = 14). To date, only 2 studies comparing IMP before and after treatment have been reported in the literature. Blackman et al studied 7 athletes with anterior CECS of the leg; no changes in IMP (63 vs 68 mm Hg; P = .15) were found, but athletes reported some pain reduction after 5 weeks of treatment with massage and stretching. Biedert and Marti, in a study of 15 patients 8 to 72 months after a fasciotomy of the deep posterior compartment of the leg, reported a 91% reduction in the average IMP (18.5 mm Hg vs 1.6 mm Hg; P = .0001) as well as a reduction in pain.

To date, surgical decompression is the only treatment for CECS recognized as curative. All other treatments are preventive or treat only the symptom. The medical approaches include reducing sports activities below the level that triggers pain or changing sports. Various physiotherapy techniques have been suggested to treat the pain, but none have had any lasting or proven efficacy. All these treatments were evaluated in studies using only posttreatment pain as the end point, not the IMP. However, because IMP is the only objective diagnostic parameter of CECS, it seemed logical to use it as the primary efficacy end point. Moreover, unlike the present study, most previous studies looked at pain reduction only, not complete elimination of pain.

In the present study, IMP measured ~4.4 months after BoNT-A injection in the 42 compartments was 59% to 69% lower than the preinjection values, with a significance level of .01 to .00001 depending on the compartment. The IMP values returned to normal in the majority of patients (87.5%, n = 14). To date, only 2 studies comparing IMP before and after treatment have been reported in the literature. Blackman et al studied 7 athletes with anterior CECS of the leg; no changes in IMP (63 vs 68 mm Hg; P = .15) were found, but athletes reported some pain reduction after 5 weeks of treatment with massage and stretching. Biedert and Marti, in a study of 15 patients 8 to 72 months after a fasciotomy of the deep posterior compartment of the leg, reported a 91% reduction in the average IMP (18.5 mm Hg vs 1.6 mm Hg; P = .0001) as well as a reduction in pain.

These results do not allow us to determine the time when IMP reduction starts or the duration of the effect of BoNT-A in lowering IMP. Further studies on the kinetics of BoNT-A are necessary to define the onset of action and total duration of efficacy of BoNT-A in lowering IMP.
Effect of Intramuscular BoNT-A Injection on Clinical Parameters

Exertional pain in CECS was considered an accessory criterion as it is a subjective functional parameter. The pain was followed up 1 month after the injection of BoNT-A, and a second evaluation was performed between 3 and 9 months (mean ± SD, 4.4 ± 1.6 months). The duration of action of BoNT-A on exertional pain beyond this period has yet to be examined. The efficacy of BoNT-A on exertional pain, measured as binary data (present or absent), may be considered positive since 15 of the 16 patients reported no exertional pain at 9 months after BoNT-A injection. The only participant who reported no pain relief had the highest IMP after the injection (P1 = 46 mm Hg and P5 = 21 mm Hg). Of note, the dose of BoNT-A used for this patient in the anterior compartment (300 U) was similar to the one used for the other 15 patients and was close to the mean value (288 ± 25 U).

The lack of previous studies using BoNT-A in this indication led us to choose the dose of BoNT-A according to our clinical experience and based on the literature. Our goal was to use the smallest dose possible in order to avoid muscle paralysis and functional impairment. This dose was one-third of the maximum recommended dose used for the treatment of lower limb spasticity,7,40 which is adjusted to the volume of the muscle to be injected and the patient’s body weight. Therefore, these initial results raise a question about the optimum dose of BoNT-A per muscle.

Motor impairment was observed in 11 of the participants, but this effect had no functional consequences and was fully reversed after 3 months in 7 patients and after 4 months in the remaining 4 patients. Therefore, BoNT-A doses should be adjusted to maintain an optimum effect on IMP and pain while causing minimal motor deficit or side effects. The safety profile was excellent; only 1 patient reported a side effect, not serious and unexplained, involving pain in the treated leg but not in the territory injected. The BoNT-A dose injected into the anterior compartment of this patient was similar to the one used for the other study participants. The causality with respect to BoNT-A is unlikely.

Regarding muscle strength, no correlation was found between the BoNT-A dose per muscle and muscle strength, but the doses injected were almost identical in all patients. The BoNT-A doses were chosen arbitrarily, based on doses used for other conditions, but this case series will help determine the doses for a future randomized, controlled study. Additionally, this study found no relation between the dose of BoNT-A injected and the reduction in IMP, probably because the doses were almost identical in all patients. We did not look for a correlation between exertional pain and the BoNT-A dose, as the total dose per patient was based on the number of affected compartments (anterior or anterolateral, unilateral or bilateral).

Plausible Pathophysiological Mechanisms of BoNT-A in CECS

The mechanism by which BoNT-A affects IMP and pain associated with CECS has yet to be determined, and several hypotheses have been suggested. Muscle fiber atrophy might be an indirect effect of BoNT-A given the reduced release of acetylcholine. The number of fibers remains unchanged, but their diameter is reduced.15,42

The first hypothesis is based on the known action of BoNT-A resulting in muscle hypotonia, which may cause moderate amyotrophy in muscles injected over a long period. This mode of action has been used for the treatment of unsightly hypertrophy of the masseter muscles and triceps surae muscles.6,21,29 Therefore, a reduction of the hypertrophy of the lower leg muscles, even if only minimal, should help reduce CECS. This action of BoNT-A was targeted in our study, and further studies using medical imaging are necessary to support this pathophysiological hypothesis.

The second hypothesis is based on the muscle relaxation induced by BoNT-A. The muscle hypotonia obtained may prolong the duration of the relaxation phase and reduce IMP,6 thereby improving blood flow to the muscles. One of the pathophysiological hypotheses formulated to explain CECS is the presence of muscle ischemia resulting in edema inside the compartment, which in turn explains the increases in IMP and in pain. Oskarsson et al,36 in a study of patients suffering from epicondylitis, showed that intramuscular BoNT-A injection in the extensor of the wrist improved blood flow in this muscle and was accompanied by pain relief. By analogy, muscle BoNT-A injection might improve blood flow in other pathological situations, such as CECS, leading to reduced IMP and pain relief. More recently, Edmundsson et al13 analyzed muscle biopsy specimens from patients during fasciotomy for CECS. The investigators showed a lower capillary supply of the tibialis anterior muscle in CECS, suggesting that local ischemia may be involved in the pathogenesis of CECS.

The third hypothesis is related to the possible analgesic action of BoNT-A, as suggested in recent studies.15,20,43 The exertional pain associated with CECS may be related to the stimulation of nociceptors in the muscles and the fascia. This action could explain the elimination of exertional pain in 94% of the patients but cannot explain the posttreatment reduction of IMP. These 3 modes of action of BoNT-A are not necessarily exclusive and could work together.

Limitations of the Study

The present study is a retrospective analysis of clinical patient files that was performed to deepen our understanding of the possible beneficial effect of BoNT-A injection in painful muscle compartments resulting from CECS. Therefore, the timing of data measurements was not set a priori and it differed between patients, leading to a large variability in the follow-up period, ranging from 3 to 9 months after BoNT-A injection. Such a study design does not allow comparison of all participants at specific time points in the recovery period but provides a view of the recovery process at different time points. Another potential weakness of the study design is that IMP and clinical parameters (ie, muscle strength and pain) were not always assessed simultaneously, which prevents direct comparison of the time course of these variables. Nevertheless, we believe that these potential limitations do not affect the main findings of the study: muscular injection of BoNT-A into painful...
compartments of study subjects with CECS characterized by abnormally elevated IMP restored normal IMP in 88% of participants and alleviated the associated muscle pain in 94% of participants. The remaining symptomatic patient was directed to fasciotomy and fully recovered. Therefore, a major outcome of this study is that a therapeutic strategy combining BoNT-A injection and (if injection is not successful) fasciotomy allowed all our patients with CECS to resume their normal level of physical activity.

Of note, the present result that BoNT-A injection lowered IMP and muscle pain was observed without dramatic impairment of muscle function, as indicated by significant but moderate reductions of Medical Research Council scores. Although muscle function might be more accurately evaluated in future studies to further ascertain the functional effect of BoNT-A injection, we believe that muscle function was mostly preserved because of the low volume of BoNT-A injected into the painful muscle compartments of our CECS patients. Although the BoNT-A dose was established from previous reports as well as the experience of our clinicians, it might well be further optimized to favor the reduction of IMP while maintaining the most muscle function.

In conclusion, the initial results of this case series showed that the intramuscular injection of BoNT-A has a short-term effect in reducing IMP and lowering exertional pain in patients with CECS in the anterior or anterolateral compartment of the leg. These encouraging results need to be confirmed by a randomized controlled study carried out over a longer period. Such a study would help define the onset and duration of action as well as the optimum dose of BoNT-A in this indication. Further studies are also necessary to define the mechanisms of action of BoNT-A on IMP and exertional pain in CECS.

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