Short-Term Effect of Low-Dose, Electromyography-Guided Botulinum Toxin A Injection in the Treatment of Chronic Lateral Epicondylar Tendinopathy

A Randomized, Double-Blinded Study

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Background: Botulinum toxin A (BoNT-A) is a novel treatment for chronic lateral epicondylar tendinopathy. Preliminary studies have demonstrated promising results; however, confirmation of the effectiveness of BoNT-A treatment and further assessment of its side effects are required. This study investigated the analgesic effects of BoNT-A in the treatment of chronic lateral epicondylar tendinopathy.

Methods: This was a phase-III, single-center, randomized, double-blinded, placebo-controlled study including 60 patients with chronic lateral epicondylar tendinopathy that had been resistant to treatment for >6 months. Patients received either a 40-IU injection of BoNT-A or saline solution placebo into the extensor carpi radialis brevis (ECRB) muscle, aided by electromyographic (EMG) stimulation. Follow-up was 3 months. The primary assessment criterion was the percentage of patients whose pain was reduced by >50% at 90 days after injection. Secondary outcomes, including pain intensity, pain frequency, interference with quality of life, sick leave taken, maximum grip strength, and side effects, were assessed at days 30 and 90, and the number of participants per group requesting additional therapies at day 90 was recorded.

Results: Twenty-nine patients in the BoNT-A group and 28 patients in the placebo group were included in the day-90 analysis. Fifteen (51.7%) of the patients who were administered BoNT-A and 7 (25%) of the patients who received placebo reported a >50% reduction in initial pain intensity at day 90 ($p = 0.005$). Pain intensity and the effect on quality of life, measured using visual analog scales, were both significantly lower in the group treated with BoNT-A compared with placebo at day 90 ($p < 0.05$). The rate of clinically detected transitory paresis of the third finger on extension was 17.2% in the BoNT-A group, with no associated functional impairment.

Conclusions: BoNT-A at 40 IU injected into the ECRB is an effective treatment for chronic lateral epicondylar tendinopathy that has been otherwise resistant to medical treatment. The rate of paresis of the third finger was low, with no associated functional impairment.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

Tennis elbow, or lateral epicondylar tendinopathy, refers to pain in the area of the lateral epicondyle of the humerus and is believed to be induced by repetitive use of the wrist and digit extensors, in particular, the extensor carpi radialis brevis (ECRB). Treatment usually consists of the use of anti-inflammatories and physiotherapy[1,2], possible immobilization with an orthosis, and local corticosteroid injection[3,4]. In 1 series, the recovery rate after 6 months was estimated at 82%[5]. However, a high level of recurrence has been observed after use of local corticosteroid injection[6].

Disclosure: The injection agent investigated in this study was supplied through a grant from the manufacturer, Ipsen. Assistance in translation of the manuscript was also supported by the grant. The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (http://links.lww.com/JBJS/E753).

Numerous treatments, based on various hypotheses[7-9], have been suggested for chronic tendinopathy, including trinitrate patches[10], acupuncture[11], neovessel sclerosis, and shock wave therapy[12,13] as well as injections with autologous blood[14-18], platelet-rich plasma[19-24], or hyaluronic acid[25]. Despite promising results from preliminary trials, these treatments require further assessment[7,26], as meta-analyses often reveal insufficient proof of effectiveness[26].

Botulinum toxin A (BoNT-A) has also been used to treat chronic lateral epicondylar tendinopathy[27-29]. We are aware of 5 randomized controlled trials that have been published[29-33]; however, the results of these studies were disparate[3,26,34,35]. The optimal injection site and dosage of BoNT-A remain unclear, and both may influence clinical results and the rate of side effects. Further study is thus required[3].

The primary objective of the present study was to assess the analgesic effects of low-dose (40 IU) BoNT-A (Dysport; Ipsen) at 3 months after injection into the ECRB with guidance from electromyographic (EMG) stimulation in the treatment of chronic lateral epicondylar tendinopathy that had been resistant to standard treatment for >6 months. The secondary objectives were to assess the incidence and level of functional impairment following low-dose BoNT-A with EMG stimulation.

Materials and Methods

Study Design

We conducted a phase-III, single-center, randomized, double-blinded, placebo-controlled clinical trial, with 3 months of follow-up. Subjects gave written informed consent, and experimental procedures were approved by the local ethics committee in accordance with the standards of the Declaration of Helsinki.

This study was registered at ClinicalTrials.gov: NCT00437762.

Patient Population

Consecutive patients who underwent consultations for chronic lateral epicondylar tendinopathy at the Orthopaedic Medicine and Rehabilitation Unit, University of Bordeaux in Bordeaux, France, were enrolled, providing they met the eligibility criteria.

Inclusion and Exclusion Criteria

Patients with a clinical diagnosis of chronic lateral epicondylar tendinopathy, confirmed through ultrasound examination, were included. The clinical diagnosis was made on the basis of lateral elbow pain, which became sharper when the origin of the lateral epicondylar muscles was kneaded and when actively extending the third digit or the wrist against resistance, with the elbow extended. The diagnosis was also based on the absence of pain both during passive elbow motion and at rest. Ultrasonographic confirmation of the diagnosis was obtained by an independent radiographer specializing in musculoskeletal imaging. An additional inclusion criterion was persistent pain (>6 months), despite medical treatment consisting of rest, analgesics, anti-inflammatories, local corticosteroid injections, and/or physiotherapy.

Exclusion criteria were an age of <18 years; suspected osteoarticular pathology of the elbow; pain of cervical origin; fibromyalgia; any conflict of interest associated with the patient's pain, including an unresolved workplace injury or ongoing legal proceedings for compensation; or postoperative symptoms. Further exclusion criteria encompassed contraindications to intramuscular BoNT-A injection, including suspected pregnancy, breastfeeding, a history of neuromuscular pathology, or current anticoagulant or aminoglycoside treatment. Patients who had received BoNT-A injections previously were excluded to avoid treatment ineffectiveness due to immunization against BoNT-A.

Number of Participants

We assumed that BoNT-A efficacy would be confirmed if, at 90 days after injection, a >50% reduction in initial pain

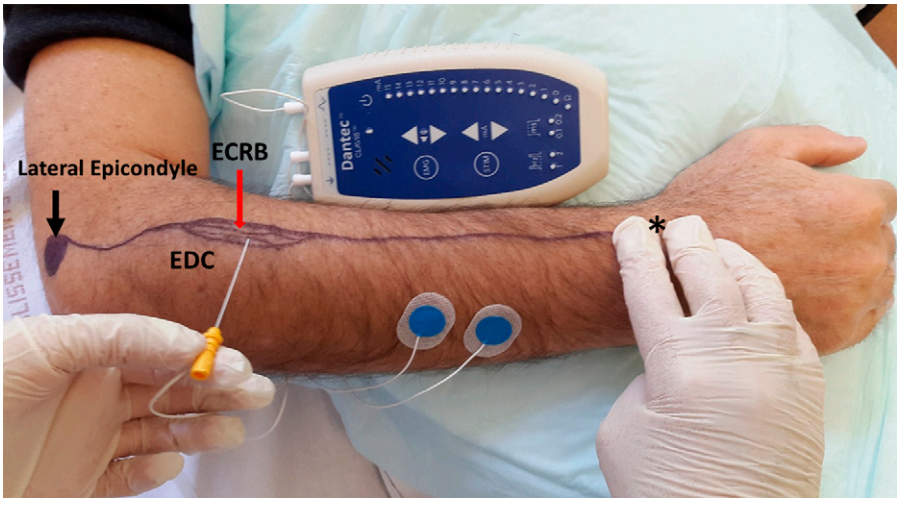

Fig. 1

Injection technique. ECRB = extensor carpi radialis brevis (red arrow), and EDC = extensor digitorum communis. The shaded area indicates the superficial zone of the muscle belly of the ECRB, and the asterisk indicates palpation of the ECRB tendon insertion into the third metacarpal with EMG stimulation.

intensity occurred in >50% of the patients receiving BoNT-A and in <30% of the patients receiving placebo. These values were selected to estimate required patient numbers using the standard formula for comparisons of 2 parallel groups of the same size (alpha risk = 5%, beta risk = 20%; power of 80%). This study thus required 28 participants in each group. To account for dropouts, 30 participants were included per group.

Randomization

Randomization (1:1) was performed after the enrollment visit, at which the patient's eligibility was confirmed (block randomization size of 4). The university pharmacist was responsible for preparation of injected products according to a randomized list, which was kept confidential. Neither therapists nor patients were aware of which product was administered.

Therapeutic Procedure

Treatments (active: 40 IU of BoNT-A from a 500-IU flask, diluted in 5 mL of saline solution; placebo: 0.4 mL of saline solution) were prepared the day of injection in a 0.4-mL syringe. The pharmaceutical laboratory of Ipsen (Beaufour Ipsen Pharma) supplied the BoNT-A. The injection site was clinically determined according to the ECRB muscular structure, at approximately 5 cm distal to the lateral epicondyle to avoid injection into the tendon[10]. Following disinfection of the skin surface using 70% alcohol, BoNT-A or placebo was administered intramuscularly into the ECRB, aided by EMG stimulation tracking using a portable EMG device (stimulation level, 2 mA) and an Ambu Neuroline Inoject hollow needle (38 × 0.45 mm, 1.5″ × 26 G; Ambu). Needle location in the ECRB was confirmed during stimulation, through observation of muscular contraction and simultaneous palpation of the

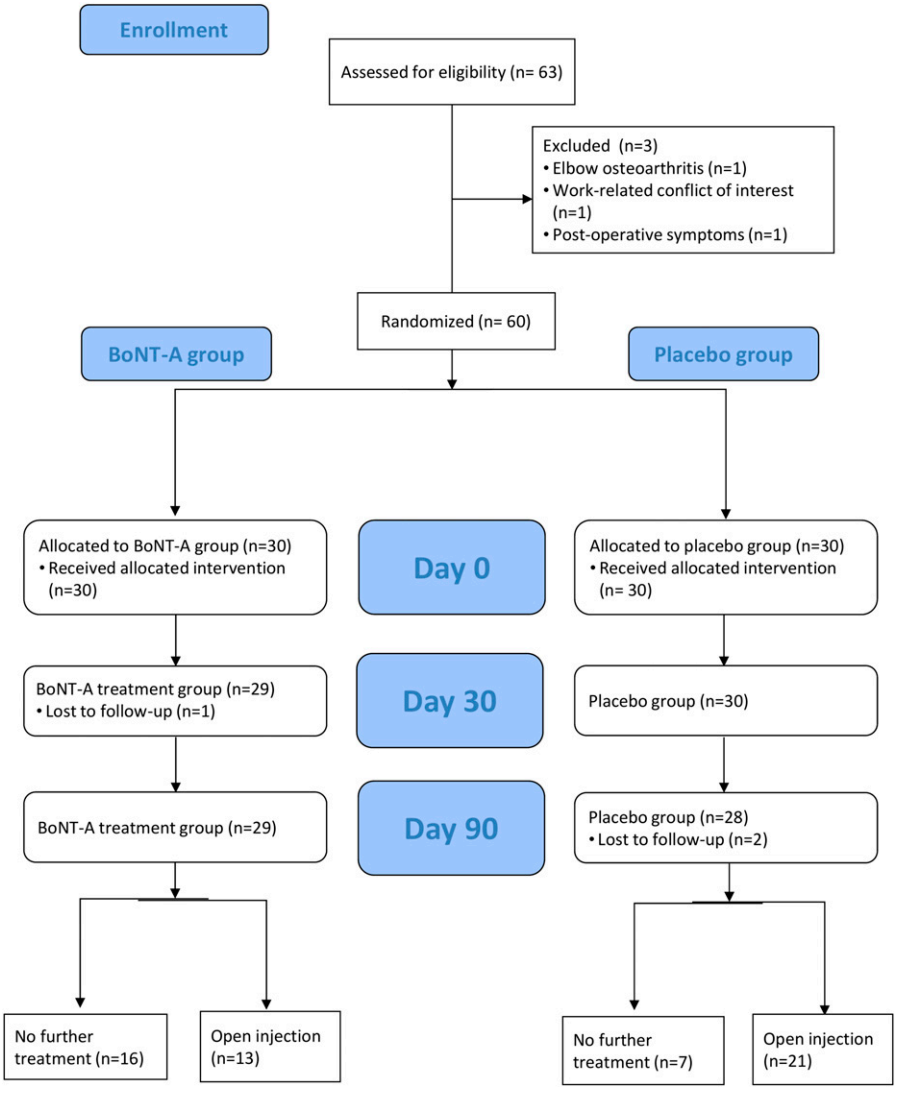

Fig. 2

Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

distal tendon of the ECRB on the lateral side of the dorsal tubercle of the radius (Lister tubercle) at the wrist (Fig. 1).

Authorized Associated Treatments

Any analgesics already being taken by patients for >6 weeks prior to enrollment were not modified. Treatment for any recurrent tendinopathy episodes following injection was standardized using a prescription combining nonsteroidal anti-inflammatory drugs and paracetamol. If the pain was not relieved at day 90, additional treatments, including injections, shock wave therapy, surgery, or open-label BoNT-A injection were offered; however, the type of injection administered at day 0 (placebo or BoNT-A) remained blinded.

Follow-up

Patients were assessed at 30 and 90 days after the initial injection.

Assessment Criteria

The primary assessment criterion was the percentage of patients whose initial pain intensity was relieved by >50% at 3 months post-injection. Pain intensity was measured using a visual analog scale (VAS) consisting of a 100-mm horizontal slide, with 0 mm indicating "no pain" and 100 mm indicating "maximum pain."

Secondary outcome criteria were assessed on days 30 and 90. In addition to the intensity of lateral epicondylar pain assessed on a VAS, pain continuity was assessed by the following question: "Rate your pain over time as 'occasional,' 'regular,' or 'constant.'" The maximum grip strength with the elbow extended was measured using a dynamometer[6]. The impact of pain on the patient's quality of life was measured on a VAS ranging from 0 mm, indicating "no interference," to 100 mm, indicating "total interference," and by assessing the percentage of patients who felt that they had been "totally cured," the number of patients on sick leave, and the number of participants in each group requesting additional therapies at day 90.

Painful or paralytic side effects were systematically evaluated in relation to duration and functional impairment and by specific clinical examination (placing the hand on a table and extending the fingers). Other side effects were identified using open-ended questions and then evaluated in terms of duration and intensity.

TABLE I Baseline Data at Day 0*

	Group		
	Placebo (N = 30)	BoNT-A (N = 30)	P Value
Age† *(yr)*	46.7 ± 6	47.3 ± 7	0.355
Female/male (no. [% female])	14/16 (46.7)	13/17 (43.3)	0.495
Duration of symptoms† *(days)*	606 ± 677	518 ± 543	0.288
VAS usual pain† *(mm)*	55.8 ± 20	56.4 ± 19	0.476
Pain frequency *(no. [%])*			0.079
Occasional	2 (6.7)	6 (20.0)	
Regular	17 (56.7)	9 (30.0)	
Constant	11 (36.7)	15 (50.0)	
Prior oral analgesic treatment *(no. [%])*	30 (100.0)	27 (90.0)	0.075
Prior physiotherapy *(no. [%])*	28 (93.3)	27 (90.0)	0.640
Prior steroid injection *(no. [%])*	27 (90.0)	28 (93.3)	0.640
Prior surgery *(no. [%])*	0 (0.0)	1 (3.3)	0.313
Interference with daily activities *(no. [%])*	26/29 (89.7)	26/30 (86.7)	1.000
Interference with sports activities *(no./no. practicing sports [%])*	5/9 (55.5)	9/19 (47.4)	0.222
Interference with professional activities *(no. [%])*	26/26 (100)	20/27 (74.1)	0.067
On sick leave *(no./no working [%])*	8/26 (30.8)	5/26 (19.2)	0.347
No. of days on sick leave†	99.8 ± 211.3	29.1 ± 78.4	0.052
VAS decrease in quality of life† *(mm)*	49.5 ± 19.0	52.0 ± 18.0	0.307
Maximum grip strength† *(N)*	30.2 ± 12.0	36.5 ± 19.0	0.139

*Statistical analysis by Student t test or chi-square test. BoNT-A = botulinum toxin A, and VAS = visual analog scale. †The values are given as the mean and the standard deviation.

TABLE II Comparison of Data at Day 30*

	Group		
	Placebo (N = 30)	BoNT-A (N = 29)	P Value
VAS usual pain† *(mm)*	45.2 ± 27.0	36.2 ± 28.0	0.099
VAS decrease in quality of life† *(mm)*	45.4 ± 21.0	35.5 ± 28.0	0.081
Maximum grip strength† *(N)*	30.3 ± 11.0	32.4 ± 19.0	0.312
Pain frequency *(no. [%])*			0.026
None	1 (3.3)	3 (10.3)	
Occasional	6 (20.0)	14 (48.3)	
Regular	16 (53.3)	5 (17.2)	
Constant	7 (23.3)	7 (24.1)	
Interference with daily activities *(no. [%])*	21/29 (72.4)	19/29 (65.5)	0.851
Interference with sports activities *(no./no. practicing sports [%])*	4/11 (36.4)	4/15 (26.7)	0.597
Interference with professional activities *(no. [%])*	22/24 (91.7)	14/26 (53.8)	0.003
On sick leave *(no./no. working [%])*	9/27 (33.3)	4/28 (14.3)	0.194
Patient feeling totally cured *(no. [%])*	0 (0.0)	7 (24.1)	0.011
Side effects *(no. [%])*	4 (13.3)	6 (20.7)	0.451

*BoNT-A = botulinum toxin A, and VAS = visual analog scale. †The values are given as the mean and the standard deviation.

Statistical Analysis

Data entry was monitored by a clinical research associate. Statistical analyses were performed using Prism 3 (GraphPad Software). A Student t test was used to analyze continuous parameters, and a chi-square test was used for categorical parameters. A p value of <0.05 was considered significant. Data are presented as the mean

TABLE III Comparison of Data at Day 90*

	Group		
	Placebo (N = 28)	BoNT-A (N = 29)	P Value
VAS usual pain† *(mm)*	42.3 ± 23	30.9 ± 22	0.032
VAS decrease in quality of life† *(mm)*	43.5 ± 26	28.4 ± 19	0.009
Maximum grip strength† *(N)*	34.2 ± 19	34.3 ± 16	0.491
Pain frequency *(no. [%])*			0.008
None	0 (0)	4 (13.8)	
Occasional	6 (21.4)	11 (37.9)	
Regular	15 (53.6)	5 (17.2)	
Constant	7 (25.0)	9 (31.0)	
Interference with daily activities *(no. [%])*	19/24 (79.2)	16/26 (61.5)	0.035
Interference with sports activities *(no./no. practicing sports [%])*	4/10 (40)	6/18 (33.3)	0.724
Interference with professional activities *(no. [%])*	19/23 (82.6)	16/26 (61.5)	0.103
On sick leave *(no./no. working [%])*	7/24 (29.2)	5/28 (17.9)	0.199
Patient feeling totally cured *(no. [%])*	1/28 (3.6)	5/29 (17.2)	0.044
Additional treatment requested *(no. [%])*	22/27 (81.5)	14/29 (48.3)	0.024
Open BoNT-A injection requested *(no. [%])*	21/27 (77.8)	13/29 (44.8)	0.012
Side effects *(no. [%])*	3/27 (11.1)	0/27 (0)	0.075

*BoNT-A = botulinum toxin A, and VAS = visual analog scale. †The values are given as the mean and the standard deviation.

and standard deviation or the percentage with the 95% confidence interval (CI).

Results

Enrollment

In total, 60 patients (33 male and 27 female; mean age, 47.0 ± 7 years) were consecutively enrolled and randomized (Fig. 2). All patients who were asked to participate in the study agreed to do so. The mean duration of chronic symptoms of lateral epicondylar tendinopathy was 18.7 ± 20 months, and the mean initial VAS score for pain was 56.1 ± 19 mm. The average impact on the patient's quality of life was assessed as 50.8 ± 18 mm on the VAS. Overall, 95% (95% CI, 86% to 99%) of the patients had previously taken nonsteroidal anti-inflammatory drugs, 92% (95% CI, 82% to 97%) had received physiotherapy, and 92% (95% CI, 82% to 97%) had received corticosteroid injections. In total, 86.7% (95% CI, 77% to 95%) of the patients reported that their condition interfered with daily activities. Baseline characteristics by study group are shown in Table I. No significant differences were observed between the groups, and no adverse effects were observed immediately following injection in either group. During follow-up, 3 patients withdrew from the study by day 90, including 1 patient who withdrew by day 30 (Fig. 2). Unblinding was not required during the study.

Day 30 Findings

At day 30, the number of patients with a >50% reduction in initial pain intensity was 9 (31.0% [95% CI, 15% to 51%]) in the BoNT-A group and 5 (16.7% [95% CI, 6% to 35%]) in the placebo group (p = 0.111). Seven (24.1% [95% CI, 10% to 42%]) of the patients in the BoNT-A group believed that their condition had been cured compared with 0 (0% [95% CI, 0% to 12%]) in the placebo group (p = 0.011). When interviewed at day 30, 5 patients reported temporary pain recurrence during the first 3 days post-injection; 1 had received BoNT-A and 4 were in the placebo group (p = 0.149). On clinical testing, 5 (17.2% [95% CI, 6% to 36%]) of the patients in the BoNT-A group had paresis of the third finger on extension compared with 0 (0% [95% CI, 0% to 12%]) in the placebo group (p = 0.021). Among the patients who worked, 4 (14.3% [95% CI, 4% to 33%]) of the patients in the BoNT-A group and 9 (33.3% [95% CI, 17% to 54%]) in the placebo group were on sick leave (p = 0.194), and the percentage of patients experiencing interference with professional activities was significantly lower in the BoNT-A group (p = 0.003). The frequency of pain was significantly less in the BoNT-A group compared with the placebo group (p = 0.026) (Table II). No significant differences between the groups were observed for quantitative parameters, including usual pain intensity, quality of life, or maximum grip strength.

Day 90 Findings

At day 90, a >50% reduction in initial pain intensity was noted for 15 (51.7% [95% CI, 33% to 71%]) of the patients who had been treated with BoNT-A and 7 (25% [95% CI, 10% to 44%]) of the patients treated with placebo (p = 0.005). Secondary parameters recorded at 3 months confirmed this significant difference (Table III). Pain intensity was significantly lower in

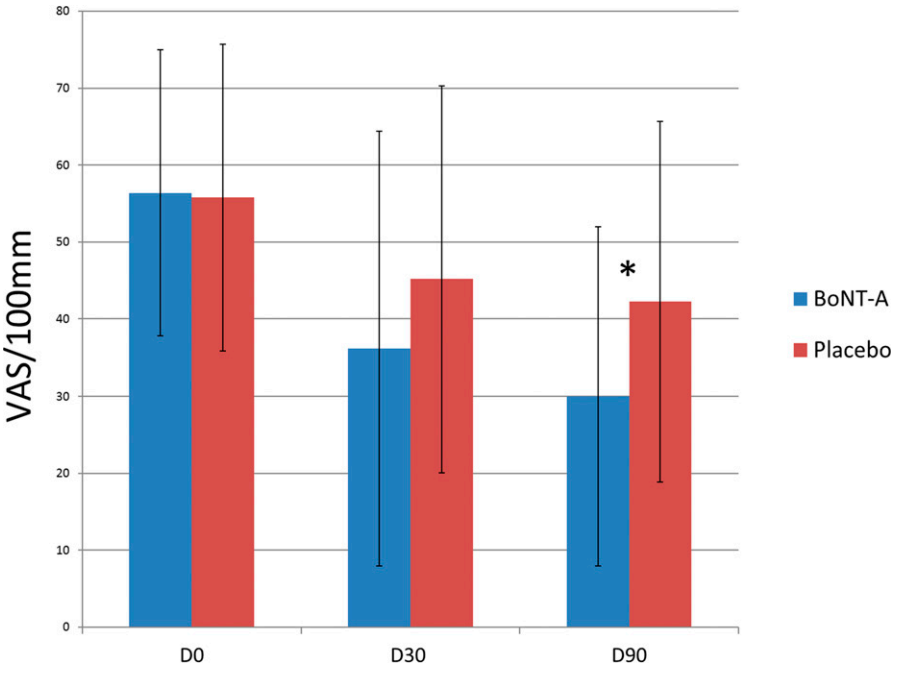

Fig. 3

Mean pain intensity in the botulinum toxin A (BoNT-A) and placebo groups. Pain intensity was assessed using a 100-mm visual analog scale (VAS; 0 mm = no pain, and 100 mm = maximum pain) and recorded at day (D) 0 and days 30 and 90 post-injection. *P < 0.05 using a Student t test. The I bars indicate the 95% confidence interval.

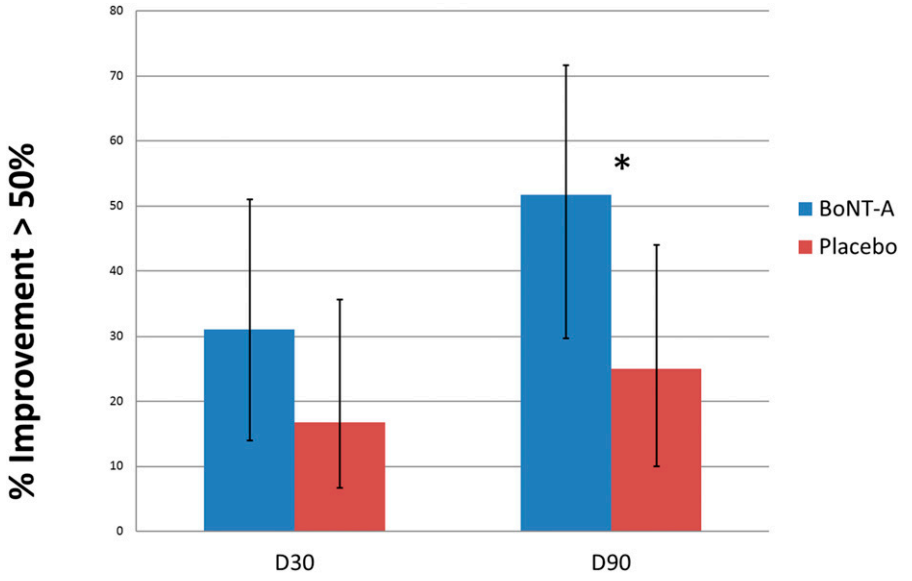

Fig. 4

Percentage of patients in the botulinum toxin A (BoNT-A) and placebo groups with pain improvement of >50% of initial pain intensity. Pain improvement was recorded at day (D) 30 and day 90 following injection. *P < 0.05 using a chi-square test. The I bars indicate the 95% confidence interval.

the BoNT-A group (p = 0.032), as was the impact of pain on quality of life (p = 0.009).

The percentage of patients who felt totally cured in the BoNT-A group (17.2% [95% CI, 6% to 36%]) was significantly higher than the percentage in the placebo group (3.6% [95% CI, 0% to 18%]) (p = 0.044). Additionally, there was a significant difference between the groups regarding ongoing pain; 15 (51.7% [95% CI, 33% to 71%]) of the patients who were administered BoNT-A reported having no more symptoms or only occasional pain compared with only 6 (21.4% [95% CI, 7% to 42%]) of the patients in the placebo group (p < 0.01). Significantly fewer patients in the BoNT-A group than in the placebo group requested additional treatment (14 of 29 patients, 48.3% [95% CI, 29% to 65%] compared with 22 of 27 patients, 81.5% [95% CI, 62% to 94%]; p = 0.024). One patient in each group requested physiotherapy, whereas all other additional treatment requests were for a BoNT-A injection. Notably, significantly more patients in the placebo group than in the BoNT-A group requested open BoNT-A injection (21 of 27 patients, 77.8% [95% CI, 58% to 91%] compared with 13 of 29 patients, 44.8% [95% CI, 26% to 64%]; p = 0.012). At day 90, 1 patient in the placebo group described persistent forearm weakness, 1 had mild finger pain, and 1 had shoulder pain, while no adverse effects were reported in the BoNT-A group. Among the patients who worked, 5 (17.9% [95% CI, 6% to 37%]) in the BoNT-A group compared with 7 (29.2% [95% CI, 13% to 51%]) in the placebo group remained on sick leave (p = 0.199).

Evolution of Pain Through Follow-up

Figures 3 and 4 show the average pain intensity in each group, measured using the VAS, over the 3-month follow-up and the percentage of patients whose initial pain was relieved by >50%. At day 30, the average pain score was lower in the BoNT-A group compared with the placebo group, but this difference was not significant. At day 90, the average pain score was significantly lower (Fig. 3) and the percentage of patients with a >50% alleviation of initial pain intensity was significantly greater (Fig. 4) in the BoNT-A group compared with the placebo group (p = 0.032 and p = 0.005, respectively).

Discussion

Our findings confirm the benefits of low-dose (40 IU) BoNT-A treatment into the ECRB, under EMG guidance, at 3 months post-injection in patients with chronic lateral epicondylar tendinopathy resistant to standard treatment for >6 months. These results are consistent with previously published reports[27,29,32,33,36]. We assessed pain relief at 30 and 90 days (Figs. 3 and 4), considering the commonly reported paralyzing effect of BoNT-A after 15 days[27,37,38].

It was hypothesized that the primary analgesic effect of BoNT-A results from an easing of tension in the entire enthesis site[39]. This muscular mechanism protects the tendon without immobilization and with early rehabilitation[40]. It is therefore likely to improve the healing process of the tendon, as observed with BoNT-A injections following surgical repair of severed tendons[41-43].

The analgesic effect observed in certain patients may be due to the inhibited release of neurotransmitters involved in tendon pain transmission[8,44-48] as well as by the inhibition of ECRB spasms, thus improving muscular blood flow and eliminating lactate responsible for pain and muscular edema[28,49].

In the present study, the ECRB was selected as the injection site, as previous studies have demonstrated the major role of its tendon in chronic lateral epicondylar tendinopathy[3,32,50-54]. Moreover, the ECRB is an accessory extensor muscle of the wrist; thus, its paralysis does not affect the patient's functional ability, unlike paresis of the extensor digitorum communis

(EDC) muscle. Indeed, the main drawback to using BoNT-A for chronic lateral epicondylar tendinopathy is possible paresis during active extension of the third finger[34,55]. When intramuscular injection was performed using clinical landmarks[30,31], an extensor lag was recorded in 66.7% to 100% of the patients. One study proposed to inject and paralyze the EDC[36], which is why all patients in that study experienced weakness of the third and fourth fingers, interfering with functioning at work. We, however, think that it is not necessary to paralyze the EDC but rather use EMG-guided injection into the ECRB.

A second major consideration when using BoNT-A is dosage. The potency ratio of Dysport to Botox (Allergan) is 1:3[56]. The BoNT-A dose used in this study (40 IU of Dysport) is lower than that used in previous studies, which ranged from 60 to >100 IU of Dysport and from 30 to 50 IU of Botox (a range of 90 to 150 IU of Dysport)[29-33]. In the present study, the rate of paresis appeared lower and less disabling compared with that in previous studies in which higher doses of BoNT-A were injected[31,32]. Moreover, with doses similar to ours, some authors[29,33] noticed significantly decreased strength of the third finger following BoNT-A injection. We believe that only 17.2% of our patients experienced transitory and mild paresis because we used a low dose and an accurate injection method. However, we used a less accurate method to assess the loss of third finger extension than did Placzek et al.[29].

By reducing the dose and targeting the ECRB, BoNT-A injection for chronic lateral epicondylar tendinopathy demonstrated positive results, with no interference with daily and work activities associated with paresis. The use of the portable EMG device[27,57] is easy and provides accuracy in administering injection into the ECRB. A novel injection procedure combining ultrasound and EMG should further limit the risk of BoNT-A spreading beyond the ECRB.

We did not identify any difference in grip strength between the 2 groups over the 3 months of follow-up. Using 50 IU of Botox (equal to 150 IU of Dysport), Lin et al.[30] found weaker grip strength in the BoNT-A group compared with a corticosteroid injection group. We think that the higher dose of Botox used in that study can explain this difference.

The major limitation of our study was that we did not assess patient-reported outcomes using a validated instrument. At the time of study design, we were not aware of a specific functional scoring system for tennis elbow. Instead, we assessed outcome using questions about pain intensity, pain continuity, and impact on quality of life as well as grip strength.

The difference between the 2 groups regarding days on sick leave at day 0 was almost significant. There were 8 patients on sick leave in the placebo group, 3 of whom were on extended leave (730 days,700 days, and 500 days), compared with 5 in the BoNT-A group on sick leave, only 1 of whom was on extended leave (365 days). This may have constituted a selection bias.

Another limitation of our study was that no psychological assessment tools were used, as has been recommended by some[58]. In addition, this was only a short-term study, and longer follow-up is needed to assess the rate of recurrence as previously reported for corticosteroid injection[6,24].

In conclusion, BoNT-A (40 IU) injected into the ECRB with EMG guidance is an effective and well-tolerated treatment for chronic lateral epicondylar tendinopathy that has been resistant to medical treatment. Treatment side effects were rare and not disabling. BoNT-A may therefore have clinical relevance as a treatment for patients whose pain from chronic lateral epicondylar tendinopathy is resistant to standard medical treatment. ■

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