Annals of Physical and Rehabilitation Medicine 62 (2019) 336–341

Available online at ScienceDirect www.sciencedirect.com

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Original article

Number of botulinum toxin injections needed to stop requests for treatment for chronic lateral epicondylar tendinopathy. A 1-year follow-up study

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ARTICLE INFO

Article history:
Received 27 April 2018
Accepted 21 December 2018

Keywords:
Tennis elbow
Epicondylar tendinopathy
Botulinum toxin A
Pain
Quality of life
Gripping force

ABSTRACT

Background: Epicondylar tendinopathy (“tennis elbow”) is a serious issue in manual labourers. Symptoms can persist over months or even more than 1 year, even when treated with trinitrine patches, acupuncture, sclerosis of neovessels, shock-wave therapy, autologous blood injections, platelet-rich plasma or hyaluronic acid. Botulinum toxin (BoNT-A) injections showed promising short-term results, but the long-term beneficial effects are not yet known.
Objective: We aimed to assess the long-term effect, side effects and recurrence rate after BoNT-A injections on chronic lateral epicondylar tendinopathy during 1 year.
Methods: This open study followed a 3-month randomized controlled trial. We included 50 patients followed at day 0 (V0), 90 (V1), 180–270 (V2) and 365 (V3). The main judgment criterion was the number of BoNT-A injections required to achieve pain relief with no further request for treatment by the patient.
Results: After one BoNT-A injection, 22/50 (44%) patients did not ask for further treatment during follow-up because of complete pain relief, and 20/50 (40%) asked for a second BoNT-A injection. For 20 patients with a second injection, 18 (90%) did not ask for further treatment during follow-up. Only 1 patient had a recurrence of pain after an initial pain relief of greater than 75%. Quality of life, and painful and maximal gripping force improved significantly at V1, V2 and V3 as compared with V0, and repercussions on daily and professional activities decreased significantly ($P < 0.05$).
Conclusions: One or 2 BoNT-A injections has favourable results for chronic epicondylar tendinopathy.
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1. Introduction

Tennis elbow, or lateral epicondylar tendinopathy (LET), describes the pain felt in the lateral epicondyle and usually occurs because of overload of that bone by repetitive use of the wrist and digit extensors, in particular the extensor carpi radialis brevis (ECRB).

As a rare occurrence, 1% to 3% per year in the overall population, tennis elbow mostly affects manual labourers (7%) [1,2]. The symptoms can persist up to more than 1 year even when treated and can have a negative impact on daily, professional or sport activities as well as overall quality of life. Patients tend to ask for multiple treatments, for a mean (median) total direct medical cost estimated at US$660 ($402) per patient over the 1-year period after diagnosis [3].

The usual treatment for this pathology is anti-inflammatory drugs, physiotherapy based on common extensor stretches [4], local immobilisation with orthosis, ultrasonography and iontophoresis. A local steroid injection [5,6] loses its effect after 3 months [7] and can even induce a high rate of recurrence in the long term [8,9].

Other treatments used are trinitrine patches [10]; acupuncture [11]; sclerosis of neovessels and shock-wave therapy [12]; injections with autologous blood [13–15], platelet-rich plasma [16–20], and hyaluronic acid [21]; and surgery [3,22–26]. Preliminary trials have shown promising results; however, meta-analyses have often revealed insufficient proof of the treatments’ effectiveness, and further evaluation is required [27].

Over the last years, botulinum toxin (BoNT-A) injections have been used [28–35] with short-term positive effects [36]. However,

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https://doi.org/10.1016/j.rehab.2018.12.003
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the long-term effects of BoNT-A injections still need to be assessed. In particular, no clinical trial has assessed how many BoNT-A injections are needed to obtain permanent pain relief and to stop requests for treatment. The main objective of the present study was to assess the number of BoNT-A injections needed to obtain long-term pain relief in patients with LET previously resistant to treatment for more than 6 months.

2. Material and methods

This was a 365-day follow-up study evaluating the long-term outcome of patients with chronic LET, following a 3-month randomized controlled trial (RCT) [37], with open injection of BoNT-A on demand by the patient at the end of the trial. The RCT, which was a superiority trial (BoNT-A vs placebo), and its long-term follow-up are reported in Clinical Trials (NCT00437762) and the trial obtained support from the French Projet hospitalier de recherche clinique, Ipsen, and the University Hospital of Bordeaux as well as approval of a French ethics committee.

The main judgment criterion in this follow-up study was the number of BoNT-A injections required to obtain pain relief and to stop requests for treatment.

2.1. Participants

All patients included in the previous RCT [37] who had received a first BoNT-A injection were included in the present study. The patients included in the RCT consulted physical and rehabilitation medicine orthopaedic pathology specialists located at the University Hospital of Bordeaux; they met the eligibility criteria and volunteered to participate in the study. They all received an information note and gave their written informed consent before the start of the study. Inclusion criteria were age $>$ 18 years old and a clinical diagnosis of chronic LET, verified by ultrasonography. The clinical diagnosis was based on the pain occurring in the lateral elbow, which became sharper when kneading the tendon insertion of the lateral epicondyle muscle and when extending the third digit or the wrist against resistance, with the elbow extended. Diagnosis also considered pain absence during passive elbow mobilisation as well as elbow pain while resting. We also looked for a pain when shaking the hand while the elbow was extended but not when it was flexed. An independent radiographer specialised in musculoskeletal imaging performed the ultrasonography diagnosis. Other inclusion criteria were: persistent pain of more than 6 months despite medical treatment consisting of rest, analgesics, anti-inflammatory drugs, local steroid injections and physiotherapy.

Exclusion criteria in the RCT were suspected osteoarticular pathology of the elbow; pain of cervical origin; fibromyalgia; any conflict of interest such as an unresolved workplace injury or ongoing compensation proceedings; all contraindications of intramuscular BoNT-A injections, including suspected pregnancy, breastfeeding, neuromuscular pathology (myasthenia, amyotrophic lateral sclerosis, myopathy and polymyositis, neuropathy); and anticoagulant or aminoglycoside treatment. Patients with a history of BoNT-A injections were excluded to avoid ineffectiveness of treatment due to previous immunisation.

2.2. Experimental procedure

2.2.1. Task

Active treatment (40IU BoNT-A Dysport®; Beaufour Ipsen Pharma, Slough, UK; from a 500 IU flask, diluted in 5 ml saline solution) was prepared on the day of injection in a 0.4 ml syringe. The injection spot was clinically determined according to the muscular structure of the ECRB, at approximately 5 cm from the lateral epicondyle to avoid intra-tendon injections. BoNT-A was administered intramuscularly into the ECRB, aided by electromyography (EMG) stimulation tracking with a portable EMG device with stimulation level 2 mA and a hollow neuroline Inoject® needle (38 × 0.45 mm, 1.5″ × 26 g; Ambu A/S, Ballerup, Denmark). We did not use echography devices in this study. The location of the needle in the ECRB was confirmed during stimulation by observing muscular contraction and simultaneous kneading of its distal tendon.

Analgesic, anticonvulsant, and antidepressant treatment that the patient was taking over 6 weeks before study inclusion was not modified. Treatment for any recurrent episodes of tendinopathy was standardised by using a prescription combining non-steroidal anti-inflammatory drugs and paracetamol. If pain was not alleviated during a visit, another treatment was offered (physiotherapy, anti-inflammatory drugs, BoNT-A injection, surgery).

The day of the first BoNT-A injection was considered the first visit (V0). The second visit (V1) was 90 days later. The third visit (V2) was scheduled at day 180 or day 270. A fourth visit (V3) was scheduled at day 365.

Because of the initial randomisation and delayed injection of the first BoNT-A injection during the RCT, 20 and 30 patients were followed up at days 270 and 365, respectively after their initial BoNT-A injection.

2.2.2. Measures

The main judgment criterion was the number of BoNT-A injections required to obtain pain relief and to stop treatment request.

Secondary assessment criteria were recorded at each follow-up visit. The pain intensity of the lateral epicondyle was measured on a visual analog scale (VAS, 0–100 mm) ranging from 0, "no pain" to 100, "maximal pain". At each consultation, patients were asked to orally evaluate the presence or absence of pain in their daily, sport, and/or professional activities. If pain was reported, the patient was asked to describe its frequency as occasional, regular or constant. The level of painful and maximal gripping force was assessed with the elbow extended by using a dynamometer, and the impact of pain on quality of life was measured on a VAS (0–100 mm) ranging from 0, "no interference" to 100, "total interference". Secondary assessment criteria also included the rate of pain reoccurrence, defined as patients, after relief of more than 75% of their initial pain 3 months after injection, experiencing a recurrence of more than 50% of their initial pain. The number of participants requiring surgery, further BoNT-A injections or physiotherapy was recorded. Painful or paralytic side effects were systematically recorded, screened, and evaluated in terms of duration and intensity (weak, mild, intense) by specific clinical evaluation (placing a hand on a table and lifting fingers). Open-ended questions assessing other side effects were asked.

3. Statistical analysis

Statistical analysis involved using Statview v5.0 (SAS Inst., Cary, NC, USA). First, the number of participants was calculated for the initial RCT [37]. Comparisons involved using Anova, then Student t test after verifying normal distribution and homogeneous variance. Chi^2 test was used to compare 2 groups. $P < 0.05$ was considered statistically significant.

4. Results

A total of 50 patients (25 women; mean age 47.68 [SD 6.91] years) received at least 1 BoNT-A injection and were consecutively included in the study (Fig. 1). In total, 27 patients had a labour

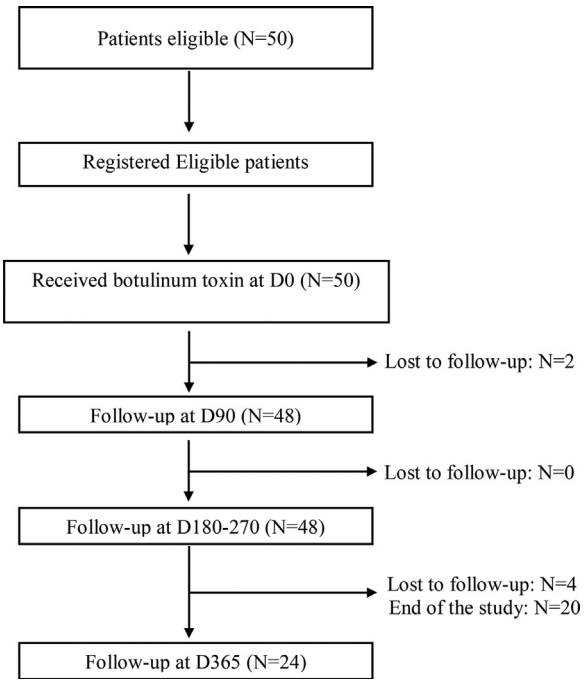

Fig. 1. Flow of participants in the study. D, day.

profession including repetitive gesture and/or carrying weight, 6 had an IT profession, and 1 a sport profession, and 3 drove a vehicle for work. The mean initial pain score (VAS) was 52.82 (SD 19.25) mm. Pain was occasional for 8, regular for 22, and constant for 20 patients. The mean duration of pain (VAS) was 631.36 (SD 662.90) days. The mean impact on quality of life was 51.38 (SD 19.09) mm.

Overall, 46/50 (92%) participants reported that their condition interfered with their daily activities (5 for grabbing an object, 19 carrying a weight, 11 domestic tasks, 2 personal hygiene, 2 using numeric devices, 1 key handling, 1 putting on a seatbelt). A total of 13/24 participants experienced difficulty with sports activities (tennis for 5, water-sport for 4, cycling for 1, martial arts for 1, dance and gymnastics for 3) and 37/44 with their professional lives. All patients had already undergone prior treatment: 47 (94%) non-steroidal anti-inflammatory drugs, 47 (94%) physiotherapy, 47 (94%) steroid injections, and 8 (4%) surgery. Ten patients were on sick leave [mean 73.00 (SD 186.5) days]. The mean painful gripping force was 20.3 (SD 12.9) Newtons and mean maximal gripping force 33.2 (SD 17.4) Newtons.

No adverse effects were observed immediately following injection.

At V0, all patients asked for a treatment and received BoNT-A injections. At V1, 24/48 (50%) patients asked for a complementary treatment: 1 (2.1%) took anti-inflammatory drugs, 4 (8.3%) received physiotherapy, 16 (33.3%) received BoNT-A injections, and 3 (6.3%) underwent surgery.

At V2, 10/48 (20.8%) patients asked for a complementary treatment: 1 (2.1%) took anti-inflammatory drugs, 2 (4.2%) received physiotherapy, 4 (8.3%) received BoNT-A injections (for 3, it was the second injection; for 1, it was the third), and 3 (6.3%) underwent surgery. No patient reported recurrence of pain.

At V3 ($n = 24$ participants), only 1 (4.2%) patient who had previously not requested any complementary BoNT-A injection but had not been released received a BoNT-A injection. One patient had a recurrence of pain, despite 2 previous BoNT-A injections at V0 and V1 with total pain relief at V2.

4.1. Cumulative effect of BoNT-A injections

Among the 50 patients receiving one BoNT-A injection, 22 (44%) did not ask for further treatment during follow-up, 2 (4%) took anti-inflammatory drugs, 5 (10%) received physiotherapy, 3 (6%) underwent surgery (lateral epicondylar release), and 20 (40%) asked for a second BoNT-A injection. For the 20 participants with a second injection, 18 (90%) did not ask for further treatment during follow-up; 1 asked for a third BoNT-A injection, and 1 underwent surgery (lateral epicondylar release). Only 1 patient had a recurrence of pain after 2 BoNT-A injections (Fig. 2).

Overall, after 1 or 2 BoNT-A injections, 40/50 (80%) patients did not ask for any further treatment because of successful and sustained pain relief, and 4 (8%) underwent surgery (lateral epicondylar release).

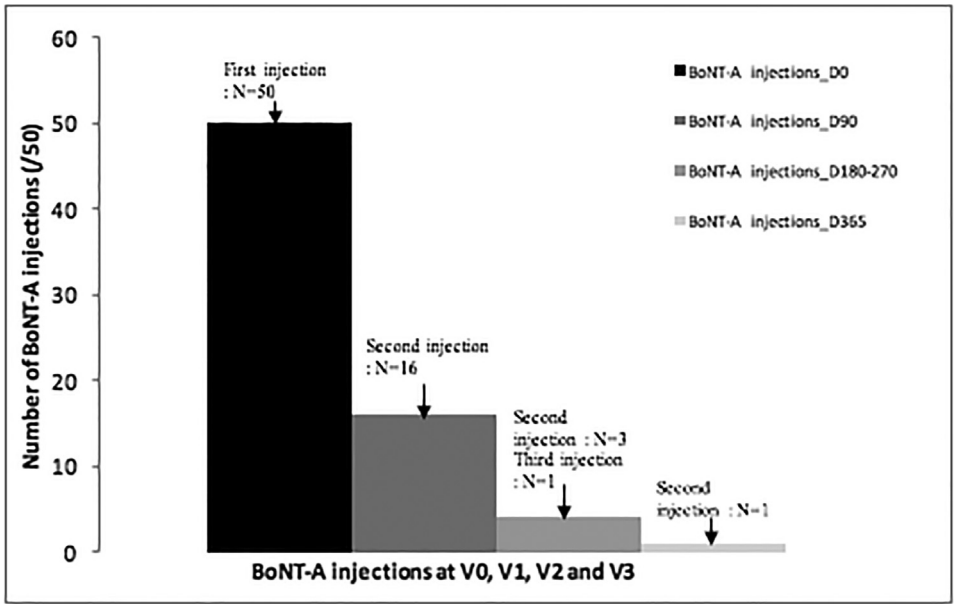

Fig. 2. Number of BoNT-A injections at the first visit (V0) and during follow-up (V1, V2, V3). Day 0 (V0), 90 (V1), 180–270 (V2) and 365 (V3).

4.2. Pain intensity at V0, V1, V2 and V3

Pain intensity significantly differed at V1, V2 and V3 as compared with V0 (Anova: F(0, 47) = 11.39, $P < 0.0001$) (Table 1). Pain score was significantly lower at V1, V2, and V3 than V0 (all $P < 0.0001$). Only 1 patient had pain recurrence at V3 despite 2 previous BoNT-A injections at V0 and V1, with total pain relief at V2.

4.3. Impact of pain on quality of life, interference of pain with daily and professional activities, and painful and maximal gripping force

Pain significantly affected quality of life at V1, V2 and V3 than V0 (Anova: F(0, 47) = 24.85, $P < 0.0001$). Quality of life was significantly less affected at V1, V2, and V3 than V0 (all $P < 0.0001$). Pain significantly interfered with daily activities at V1, V2 and V3 than at V0 (Anova: F(0, 47) = 21.44, $P < 0.0001$). Pain interfered less with daily activities at V1, V2 and V3 than V0 (all $P < 0.0001$). Pain significantly interfered with professional activity at V1, V2 and V3 than V0 (Anova: F(0, 47) = 12.14, $P < 0.0001$). Pain interfered less with professional activity at V1 than V0 ($P < 0.05$), V2 than V0 ($P < 0.0001$) and V3 than V0 ($P < 0.0001$). Painful gripping force significantly differed at V1, V2 and V3 than V0 (Anova: F(0, 47) = 14.99, $P < 0.0001$). Painful gripping force was significantly lower at V0 than V1, V2 and V3 (all $P < 0.0001$). Maximal gripping force significantly differed in comparing V0, V1, V2 and V3 (ANOVA: F(0, 47) = 4.35, $P < 0.01$). Maximal gripping force was significantly lower at V0 than V2 ($P < 0.05$) and V3 ($P < 0.01$). Maximum force did not differ between V0 and V1 ($P = 0.48$).

Table 1
Decrease of pain at follow-up: day 90 (V1), 180–270 (V2) and 365 (V3) compared to day 0.

	V1 ($n = 48$)	V2 ($n = 48$)	V3 ($n = 24$)
Decrease of pain more than 75% of the initial pain	9 (19)	22 (46)	15 (63)
Decrease of pain more than 50% of the initial pain	20 (42)	31 (65)	18 (75)
Decrease of pain between 1% and 50% of the initial pain	13 (27)	10 (21)	4 (17)
No decrease of the initial pain	15 (31)	7 (14)	2 (8)

Data are *n* (%) or patients.

4.4. Comparison between participants on sick leave and other participants

At V0, all patients on sick leave reported that pain interfered with their professional activities (versus 76% of the other participants, $P < 0.01$). The impact of pain on quality of life (VAS) was greater for patients on sick leave than others (64.5 [SD 21.40] vs 48.1 [SD 17.24] mm, $P < 0.05$) (Table 2).

At V1, painful gripping force was lower for patients on sick leave than others [13.56 (SD 8.52) vs 32.14 (SD 18.40) N, $P < 0.001$], as was maximal gripping force [19.67 (SD 8.86) vs 39.73 (SD 17.62) N, $P < 0.01$]; all patients on sick leave continued physiotherapy, whereas 2 of the other participants stopped physiotherapy ($P < 0.05$).

At V2, painful gripping force was lower for patients on sick leave than others [29.44 (SD 13.79) vs 44.17 (SD 23.59) N, $P < 0.01$], as was maximal gripping force [30.56 (SD 12.36) vs 47.06 (SD 22.51) N, $P < 0.01$]; none of the participants on sick leave asked for a BoNT-A injection at V2, whereas 4 other patients asked for another injection ($P < 0.05$).

At V3, the 2 groups did not differ in variables (Table 2).

4.5. Side effects

At V1, 3 patients presented slight weakness at the wrist or finger level (during 90, 86, and > 60 days). At V2, 4 patients presented slight or moderate weakness at the finger level (during 16, 153, and 68 days; duration not known for the fourth participant), 1 patient had a slight headache, 1 had foot pain, and 1 had a heart attack (non-fatal). At V3, 1 patient had moderate weakness at finger level. The side effects of heart attack, headache and foot pain were not attributed to BoNT-A injections. Patients did not complain of weakness at the wrist or finger level, but this was detected by specific clinical evaluation (see Methods).

5. Discussion

Our study shows a homogeneous and sustained effect of BoNT-A injections on pain and functional repercussions of pain during 1 year in 50 patients, with a weak rate of recurrence after initial relief. After one BoNT-A injection, 44% patients did not ask for further treatment during follow-up, and 40% asked for a second BoNT-A injection. After 2 BoNT-A injections, 90% of patients did not ask for further treatment during follow-up. Thus, after 1 or 2 BoNT-A injections, 80% of patients did not ask for any further treatment because of successful and sustained pain relief. Quality of life was

Table 2
Pain; constancy of pain; repercussion on quality of life, daily-, sport- and professional activities; sick leave; and gripping force.

	V0 ($n = 50$)	V1 ($n = 48$)	V2 ($n = 48$)	V3 ($n = 24$)	Results Anova
Pain, VAS (0–100 mm), mean (SD)	52.8 (19.3)	31.7 (22.3)	23.7 (25.9)	15.0 (20.0)	F(0,47) = 11.39, η2partial = 1.00, $P < 0.001$
Constancy of pain (% of patients)					
No pain	0	12.5	27.1	37.5	F(0,47) = 3.51, η2 partial = 0.78, $P < 0.05$
Occasional pain	16.0	43.8	47.9	45.8	F(0,47) = 0.063, η2 partial = 0.061, $P = 0.98$
Regular pain	44.0	18.75	14.6	8.3	F(0,47) = 0.99, η2partial = 0.26, $P = 0.40$
Constant pain	40.0	25.00	10.4	8.3	F(0,47) = 2.038, η2partial = 0.51, $P = 0.11$
Repercussion on quality of life, VAS (0–100 mm), mean (SD)	51.4 (19.1)	28.3 (21.7)	19.3 (24.2)	14.0 (20.3)	F(0,47) = 24.85, η2partial = 1.00, $P < 0.001$
Repercussion on (% of patients)					
Daily activities	92.0	54.2	44.7	15.8	F(0,47) = 21.44, η2partial = 1.00, $P < 0.001$
Sport activities	54.2	33.3	22.7	20.0	F(0,47) = 2.39, η2partial = 0.57, $P = 0.075$
Professional activities	84.1	64.3	32.5	40.0	F(0,47) = 12.14, η2partial = 1.00, $P < 0.001$
Sick leave (% of patients)	21.7	21.7	15.2	0.0	F(0,47) = 2.06, η2partial = 0.51, $P = 0.11$
Gripping force (Newtons), mean (SD)					
Painful	20.3 (12.9)	28.4 (18.4)	41.2 (22.6)	45.6 (20.5)	F(0,47) = 14.99, η2partial=,1.00 $P < 0.001$
Maximal	33.2 (17.4)	35.8 (18.1)	43.8 (21.8)	47.6 (20.4)	F(0,47) = 4.35, η^2partial = 0.87, $P < 0.01$

VAS: visual analog scale.

improved significantly at V1, V2 and V3 versus V0. In particular, pain and interference of pain with daily and professional activities decreased significantly at V1, V2 and V3 versus V0 (Table 1). Our findings suggest using BoNT-A injections in patients with chronic LET [persistent pain > 6 months (mean 631.36 [SD 662.90]) days] despite medical treatments: rest, analgesics, anti-inflammatories, local steroid injections, physiotherapy. They also indicate a long-lasting effect of BoNT-A on chronic LET, with a small rate of pain recurrence (1 patient at day 365). These results confirm the beneficial long-term effect of BoNT-A injections reported in a comparative study with surgery [38].

The differences between V0, V1, V2 and V3 concerning the repercussions on sport activities and the number of participants on sick leave were not significant. We attribute these observations to the low number of patients who reported sport repercussion (24 patients) or were on sick leave (10 patients) at inclusion.

Most of the studies of BoNT-A injections and chronic LET ended after a 3-month follow-up without investigating the long-term success of the treatment. This study indicates a low rate of recurrence after pain relief with BoNT-A injections. In 40% of cases, 2 BoNT-A injections were required.

Three patients asked for surgery at V1; these participants had a similar profile: they all had long-term chronic LET (mean duration 513 days), with daily-life repercussions for all and professional repercussion for 2. All had tried anti-inflammatory drugs, physiotherapy and infiltration before BoNT-A injections. Pain did not change between V0 and V1 for 2, and even increased for the third. None of these participants declared any side effects during follow-up. Further studies could determine whether patients with failed BoNT-A injections had a similar profile. Nevertheless, the superiority of surgery for BoNT-A injections in patients with chronic epicondylar tendinopathy has not been proven [36].

The primary analgesic effect of BoNT-A is suggested to result from easing the tension in the whole enthesis site, including the tendon [36], thereby resulting in immobilisation of the enthesis. This procedure has been shown to improve the healing process of several tendons [40,41]. BoNT-A is also said to have an analgesic effect by inhibiting the release of neurotransmitters such as glutamate, substance P and calcitonin gene-related peptide involved in the transmission of tendon pain [42]. The need for a longer rest period could also explain the requirement of a second BoNT-A injection.

The dose of BoNT-A used in this study was lower than in previous studies [32,34,35], which could explain why no patient reported weakness at the wrist or finger level, why only 8 patients had a paresis at the wrist or finger level in a specific clinical evaluation, and why the maximal gripping force improved significantly during the follow-up, which is also an indirect sign of healing of a tendon.

However, this study has some limitations. The RCT stopped at day 90, followed by an open study. Nevertheless, this was a longer follow-up than most of the previously published studies. The evaluation of pain involved only the VAS, because the Patient-rated Tennis Elbow Evaluation Questionnaire was not validated in French at the inclusion time [43]. We did not search for pain when the tendon was passively stretched, which could have been done. We did not monitor participants' compliance with the rehabilitation self-exercise program given at each visit, which could be a factor of variation between participants. We could have evaluated anxiety and depression in this population (e.g., by using the Hospital Anxiety and Depression scale), to search for predictive factors of non-response to the treatment. In further studies, the injected muscles after injections could be explored by imaging, to determine whether these muscles had a fatty involution and to search for another explanation in patients with persistent pain.

In conclusion, this study validated the long-term effectiveness of 1 or 2 BoNT-A injections in chronic LET and it places injections as a first choice if the pain is resistant to well-conducted standard medical treatment.

Funding

The Ipsen company co-funded this study within the French Hospital Clinical Research Project (PHRC Project) framework. The funding sources did not play any role in investigation.

Disclosure of interest

Ipsen company co-funded the study (co-financing with 5000 euros), as well as the French Hospital Research Project (PHRC Project) framework, but Ipsen company did not interfere with the inclusions nor with the data statistical analysis nor with the writing of the article..

Acknowledgment

The authors thank Anna Moraïtis for copy-editing the manuscript.

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