

Treatment of Lateral Epicondylitis with Botulinum Toxin

A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: Lateral epicondylitis is a common condition for which botulinum toxin has been reported to have a therapeutic role in uncontrolled studies.

Objective: To determine if an injection of botulinum toxin is more effective than placebo for reducing pain in adults with lateral epicondylitis.

Design: Randomized, double-blind, placebo-controlled trial conducted from September 2002 to December 2004.

Setting: Outpatient clinics at a university hospital and a district hospital in Hong Kong.

Participants: 60 patients with lateral epicondylitis.

Measurements: The primary outcome was change in subjective pain as measured by a 100-mm visual analogue scale (VAS) ranging from 0 (no pain) to 10 (worst pain ever) at 4 weeks and 12 weeks. All patients completed post-treatment follow-up.

Interventions: A single injection of 60 units of botulinum toxin type A or normal saline placebo.

Results: Mean VAS scores for the botulinum group at baseline and at 4 weeks were 65.5 mm and 25.3 mm, respectively; respective scores for the placebo group were 66.2 mm and 50.5 mm

(between-group difference of changes, 24.4 mm [95% CI, 13.0 to 35.8 mm]; $P < 0.001$). At week 12, mean VAS scores were 23.5 mm for the botulinum group and 43.5 mm for the placebo group (between-group difference of changes, 19.3 mm [CI, 5.6 to 32.9 mm]; $P = 0.006$). Grip strength was not statistically significantly different between groups at any time. Mild paresis of the fingers occurred in 4 patients in the botulinum group at 4 weeks. One patient's symptoms persisted until week 12, whereas none of the patients receiving placebo had the same complaint. At 4 weeks, 10 patients in the botulinum group and 6 patients in the placebo group experienced weak finger extension on the same side as the injection site.

Limitations: The trial was small, and most participants were women. The blinding protocol may have been ineffective because the 4 participants who experienced paresis of the fingers could have correctly assumed that they received an active treatment.

Conclusions: Botulinum toxin injection may improve pain over a 3-month period in some patients with lateral epicondylitis, but injections may be associated with digit paresis and weakness of finger extension.

Ann Intern Med. 2005;143:793-797.

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ClinicalTrials.gov Identifier: NCT00119704

Tennis elbow (lateral epicondylitis), a common cause of chronic elbow pain and wrist extensor dysfunction in adults, affects 1% to 3% of the general population each year (1). Localized tenderness around the lateral epicondyle generally characterizes the condition, and pain can be reproduced by resisted extension of the wrist or middle finger with the elbow in a straight position. There is currently no consensus on optimal treatment, but numerous options are available. The best-available scientific evidence suggests that topical and possibly oral nonsteroidal anti-inflammatory drugs may be the most useful for short-term pain relief. Corticosteroid injections may be beneficial as a temporary measure but carry the risk for possible adverse effects (2). Botulinum toxin has been used in the treatment of lateral epicondylitis with promising results, but the positive response cannot necessarily be attributed to the intervention because of the lack of control groups in these studies (3, 4). Consequently, we conducted a randomized, double-blind, placebo-controlled trial to determine if an injection of botulinum toxin type A reduces pain more effectively than placebo in adults with lateral epicondylitis.

METHODS

Study Sample and Setting

In this double-blind, placebo-controlled trial, patients were randomly assigned to receive injections of botulinum

toxin or a saline placebo. Ethics approval was obtained from the institutional review boards, and patients gave written informed consent. The rationale of the study and the potential for side effects, such as arm or finger weakness, were explained to all patients.

We recruited consecutive patients with tennis elbow who were 18 years of age or older and who were newly referred to the medical outpatient clinics at the authors' institutions from September 2002 to December 2004. The Prince of Wales Hospital is a 1200-bed university hospital that serves a surrounding population of 600 000 and receives an equal mix of secondary and tertiary referrals. The North District Hospital is a 600-bed community hospital that serves a surrounding population of 300 000, predominantly through secondary referrals but also through some

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Context

Do botulinum toxin injections help or hurt patients with tennis elbow?

Contribution

Sixty adults with pain from lateral epicondylitis that had persisted for longer than 3 months were randomly assigned to receive a single injection of botulinum toxin or normal saline. Pain scores, which were assessed 4 and 12 weeks later, were significantly lower in the botulinum group than in the group receiving saline injections. Four weeks after the injections were administered, the investigators observed finger extension weakness in 10 patients in the botulinum group versus 6 patients in the saline group. Four of the patients who received the botulinum toxin also experienced digit paresis.

Implications

We need larger, longer trials to establish the benefits (degree and duration of pain relief) and harms of botulinum injections for tennis elbow.

—The Editors

tertiary referrals. One of 2 investigators, both of whom are board-certified general internists, evaluated each patient candidate to determine eligibility for participation. Inclusion criteria were pain at the lateral side of the elbow that had persisted for longer than 3 months and pain at the lateral epicondyle during resisted dorsiflexion of the wrist with the elbow in full extension. Exclusion criteria were

previous local injection treatments (including corticosteroid injections and acupuncture therapy for this particular condition); nerve entrapment; pregnancy; breastfeeding; and systemic neuromuscular disorders, such as myasthenia gravis.

Randomization and Intervention

The researchers assigned patients to groups by using a computer-generated randomization sequence with a permuted block size of 3, stratified by center. Participants were assigned to receive 60 units of Dysport botulinum toxin (Beaufour Ipsen International, Maidenhead, United Kingdom) or an equivalent volume of normal saline. The randomization assignments were placed in opaque envelopes that were kept by a research assistant who commuted between the 2 centers and drew up the injections according to the randomization schedule. The assistant used micro-pore taping over the syringes to ensure that the person administering injections was blinded to allocation status. With the patient flexing the affected arm and resting it on a firm surface, an investigator administered the injection. Patients with bilateral symptoms received injections in both arms. Injections were administered deeply into the subcutaneous tissue and muscle, 1 cm from the lateral epicondyle, and were aimed toward the tender spot.

Outcomes and Follow-up

Before randomization, a research assistant recorded relevant baseline demographic data, including weight, height, dominant hand, and duration of symptoms. The primary end point was pain intensity as assessed by a 100-mm visual analogue scale (VAS) ranging from 0 (no

Figure. Study flow diagram.

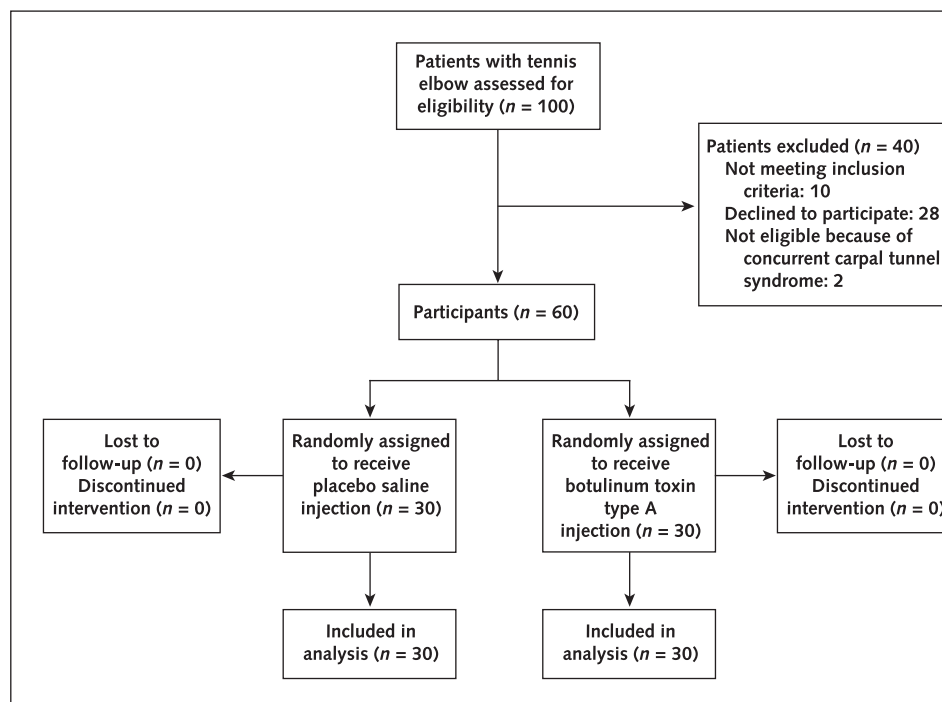


Table 1. Summary of Patient Demographic Data and Baseline Characteristics

Characteristic	Botulinum Toxin Group (n = 30)	Placebo Group (n = 30)
Mean age (SD), y	45.60 (9.06)	44.18 (5.72)
Sex, n		
Women	25	24
Men	5	6
Dominant hand, n		
Right	29	29
Left	1	1
Mean body mass index (SD), kg/m ²	22.74 (3.28)	23.22 (3.02)
Location of symptoms, n		
Left elbow	11	10
Right elbow	17	14
Both elbows	2	6
Duration of symptoms, mo		
Mean (SD)	11.83 (9.51)	19.07 (21.05)
Median	9.0	8.50
Minimum–maximum	4–42	6–72
Pain intensity (SD), mm*	65.5 (15.0)	66.2 (13.2)
Grip strength (SD), kg		
Right side	20.29 (5.27)	23.81 (7.28)
Left side	19.56 (5.46)	20.06 (6.60)

* Pain intensity as measured by a 100-mm visual analogue scale.

pain) to 10 (worst pain ever). Patients with bilateral symptoms were asked to identify the side on which symptoms were worse and to grade only the pain experienced on that side. Grip strength, a secondary outcome, was measured with a Jamar hydraulic hand dynamometer (Sammons Preston, Bolingbrook, Illinois). The assessment was conducted with the patient's elbow fully extended and the dynamometer's handle set to the middle position. After each patient performed the grip test 3 times on the affected

arm, the mean score was calculated and used for analysis. Grip strength and VAS scores were recorded at baseline, 4 weeks, and 12 weeks.

We instructed participants to avoid pain-provoking activities as much as possible for 48 hours after receiving the injections. We also asked patients to stop all other treatments for tennis elbow and to avoid co-interventions, such as nonsteroidal anti-inflammatory drug therapy, physical therapy, and alternative medicines, for the course of the trial. During follow-up evaluations at 4 and 12 weeks, we explicitly queried patients about the presence of any weakness and whether any symptoms were sufficiently severe to affect workday activities. At these visits, we also used open-ended questions to ask about other potential adverse effects. Two physicians reviewed the other reported symptoms to determine whether they might be related to the injections.

Statistical Analysis

We estimated that a sample size of 60 was needed to achieve 80% statistical power to detect a 40% difference in VAS scores between the treatment groups at a statistical significance level of 0.05. Our calculations were based on findings from a previous study comparing corticosteroid therapy with placebo, which reported a 40% difference in VAS scores at 4 weeks. We assumed that the placebo group would achieve a 30% reduction in pain intensity within this time frame, and we hypothesized that a botulinum injection would provide at least the same degree of improvement as corticosteroid therapy (5). We know of no universally accepted clinical outcome measure for patients with lateral epicondylitis; if we adhere to the standards for gauging therapeutic response in other rheumatic diseases, however, we might assume that a 20% improvement in VAS scores over baseline values represents a minimum requirement for the response to be clinically important (6). We used a 1-sample Kolmogorov–Smirnov test, probabili-

Table 2. Summary of the Outcome Measurements between the Study Groups

Evaluation	Mean (SD)		Difference between Groups (95% CI)	P Value
	Botulinum Toxin Group (n = 30)	Placebo Group (n = 30)		
Pain intensity, mm*				
Baseline	65.5 (15.0)	66.2 (13.2)		
Week 4	25.3 (18.8)	50.5 (21.7)	24.4 (13.0 to 35.8)	<0.001†
Week 12	23.5 (22.3)	43.5 (23.9)	19.3 (5.6 to 32.9)	0.006†
Grip strength, kg				
Right side				
Baseline	20.29 (5.27)	23.81 (7.28)		
Week 4	17.47 (4.47)	23.13 (7.39)	2.14 (–1.65 to 5.92)	0.259
Week 12	20.65 (4.89)	24.75 (7.35)	0.58 (–3.08 to 4.25)	0.742
Left side				
Baseline	19.56 (5.46)	20.06 (6.60)		
Week 4	18.75 (7.99)	21.41 (6.36)	2.17 (–1.32 to 5.64)	0.214
Week 12	21.31 (6.96)	22.12 (6.02)	0.31 (–2.40 to 3.02)	0.818

* Pain intensity as measured by a 100-mm visual analogue scale.

† Statistically significant.

Table 3. Reports of Adverse Events

Adverse Event	Botulinum Toxin Group (n = 30), n	Placebo Group (n = 30), n	Total (n = 60), n
Postinjection			
Pain	2	1	3
Nausea	0	1	1
Week 4			
Weakness in finger extension	10	6	16
Paresis of digits	4	0	4
Week 12			
Weakness in finger extension	2	1	3
Paresis of digits	1	0	1
Total	19	9	28

ty-probability plots, and quantile-quantile plots to confirm normality. We used 2-sample *t*-tests to compare changes of VAS score and grip strength at baseline, week 4, and week 12. All *t*-tests were 2-sided with a significance level of 0.05. We performed analyses using SPSS software, version 10.0 (SPSS Inc., Chicago, Illinois).

Role of the Funding Source

This study was funded by a donation from New World Development Ltd. The sponsor had no part in the design of the study, collection of data, data interpretations, or final manuscript preparation. The authors had full access to the study's data and were responsible for statistical analysis, reporting of data, and manuscript submission.

RESULTS

Of 100 patients with lateral epicondylitis who were referred to the clinics, 88 met eligibility criteria and 60 agreed to participate in the trial (Figure). Most participants were middle-aged women whose symptoms had persisted for several months (Table 1). Most baseline characteristics for the 2 groups appeared to be similar. Table 2 shows mean scores for the VAS at baseline and at each follow-up assessment. At 4 weeks, the botulinum group showed a statistically significant improvement in VAS pain assessments over the placebo group ($P < 0.001$), which was maintained at 12 weeks ($P = 0.006$). The mean VAS scores were 65.5 mm and 25.3 mm at baseline and at 4 weeks for the botulinum group and 66.2 mm and 50.5 mm for the placebo group, respectively (between-group difference of changes, 24.4 mm [95% CI, 13.0 to 35.8 mm]). At week 12, the mean VAS scores were 23.5 mm for the botulinum group and 43.5 mm for the placebo group (between-group difference of changes, 19.3 mm [CI, 5.6 to 32.9 mm]). Grip strength was not statistically significantly different between groups at any time.

All reported side effects are summarized in Table 3. Ten patients in the botulinum group had mild weakness of finger extension in the injected arm at 4 weeks; 2 patients reported persistent weakness at 12 weeks. In the placebo

group, 6 patients had weakness at 4 weeks and 1 person reported persistent weakness at 12 weeks. Only 1 person in the botulinum group reported weakness sufficient to interfere with work activities. Four patients had paresis of the second to fourth digits at 4 weeks in the botulinum group, whereas no instances of paresis were observed in the placebo group. Two patients in the treatment group and one in the placebo group reported mild postinjection pain for as long as 2 weeks. No patients in either group reported using nonsteroidal anti-inflammatory drugs, physical therapy, or other treatments that could have affected outcome.

DISCUSSION

Our findings suggested that botulinum toxin injection was superior to placebo injection for reducing pain over a 12-week period in patients with lateral epicondylitis. The most common adverse events were weakness of finger extension and paresis of digits, with 1 patient reporting paresis that persisted for 3 months. We found that the lower bound of the CI for the between-group differences in mean VAS pain scores at 12 weeks was 5.6 mm. If we assume that a 20% or greater improvement of VAS scores represents a minimally important therapeutic response (6), we cannot exclude the possibility that botulinum is not superior to placebo in substantively reducing pain associated with lateral epicondylitis. The wide bounds of the CIs that we found may be attributable to the modest size of the trial; alternatively, positive beneficial effects of botulinum toxin on pain may be transient and may not extend beyond a few weeks.

If we assume that the potency ratio of Dysport to Botox (Allergan, Inc., Irvine, California) is 1:3, our dosing was similar to that of previous studies (3, 4). We used a clinical landmark for injection in our trial, whereas a previous study used electromyographic guidance (3). Although electromyographically guided injections theoretically ensure more accurate placement of the botulinum toxin and reduce the dosage requirement, our clinical injection method mirrors daily practice, where electromyography may not be readily available (7).

In a recently published study of 40 patients with tennis elbow that compared botulinum toxin injection with a normal saline placebo, Hayton and colleagues (8) found no statistically significant difference between groups in pain and mean grip strength. This "negative" result may have several explanations. First, a true clinical difference between groups may not have been detected because of the small sample size leading to a type II error; absence of evidence is not evidence of absence (9). Second, Hayton and associates recruited patients whose symptoms had not responded to conservative treatment whereas we excluded patients who had previously received corticosteroid injections. Last, the investigators for the earlier study used injection sites that were located further from the lateral epicondyle than those used in our study.

Although botulinum toxin has been used in various pain syndromes (10), its exact mechanism for relieving pain remains largely unknown (11–14). One plausible explanation is that the paralytic effect of botulinum toxins forces the extensor group of muscles to rest for a period of 2 to 4 months, thereby allowing the tendon fibers close to the lateral epicondyle time to repair. This effect may have been partially reflected by the changes in mean grip strength that showed a decrement at 4 weeks before recovering as the botulinum toxins wore off (Table 2). Interpretation of the grip strength data, however, might not be straightforward because the trial involved few participants; consequently, influences of any gender and dominant hand effects on grip strength findings could not be fully evaluated.

Our study has 3 possible limitations. First, we conducted our research in a tertiary referral setting; therefore, findings might not apply to community settings where patients might have different manifestations of epicondylitis and physicians might have different skills and experience in injecting elbows. The severity of our participants' symptoms was above average because the mean disease duration was 12 months for the botulinum group and 19 months for the placebo group. Second, true blinding might not have occurred in a few patients because the botulinum toxin induced finger weakness and paresis of the extensor muscles group, although only 1 patient reported paresis. Third, most participants were women; therefore, we do not know if the results may be extrapolated to men.

With few scientifically proven treatments for tennis elbow, botulinum toxin may offer an alternative short-term treatment option for some patients. The issue of possible arm weakness and paresis of the extensor muscle group should be discussed with patients before any trial injections are administered, however (3, 4, 8). Additional studies are needed to better identify the magnitude and duration of pain relief associated with different doses of botulinum. The frequency, severity, and duration of adverse effects must also be investigated.

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Grant Support: By a donation from New World Development Ltd.

Potential Financial Conflicts of Interest: None disclosed.

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Obtaining of funding: S.M. Wong.

Administrative, technical, or logistic support: S.M. Wong, P.-Y. Tong, D.W.F. Poon.

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