

Authors:

Yu-Ching Lin, MD, MSc
Yuan-Kun Tu, MD
Sheng-Shiung Chen, BSc
I-Ling Lin, BSc, MSc
Shih-Ching Chen, MD, PhD*
How-Ran Guo, MD, MPH, ScD*

*These authors contributed equally to this work.

Affiliations:

From the Department of Physical Medicine and Rehabilitation (Y-CL, S-SC), E-Da Hospital, Kaohsiung, Taiwan; Department of Physical Therapy (Y-CL), I-Shou University, Kaohsiung, Taiwan; Department of Environmental and Occupational Health (Y-CL), National Cheng Kung University, Tainan, Taiwan; Department of Orthopedic (Y-KT), E-Da Hospital, Kaohsiung, Taiwan; Department of Biomedical Engineering (Y-KT), I-Shou University, Kaohsiung, Taiwan; Departments of Physical Medicine and Rehabilitation (S-CC), Taipei Medical University Hospital, Taipei, Taiwan; Departments of Physical Medicine and Rehabilitation (S-CC), Taipei Medical University, Taipei, Taiwan; Department of Biomedical Laboratory Science (I-LL), Kaohsiung Medical University, Kaohsiung, Taiwan; and Department of Environmental and Occupational Health (H-RG), College of Medicine, National Cheng Kung University; Center for Occupational and Environmental Health and Preventive Medicine (H-RG), National Cheng Kung University; Department of Occupational and Environmental Medicine (H-RG), National Cheng Kung University Hospital, Tainan, Taiwan.

Correspondence:

All correspondence and requests for reprints should be addressed to: How-Ran Guo, MD, MPH, ScD, Department of Environmental and Occupational Health and Preventive Medicine, College of Medicine, National Cheng Kung University, 138 Sheng-Li Road, Tainan 70428, Taiwan.

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ORIGINAL RESEARCH ARTICLE

Comparison Between Botulinum Toxin and Corticosteroid Injection in the Treatment of Acute and Subacute Tennis Elbow

A Prospective, Randomized, Double-Blind, Active Drug-Controlled Pilot Study

ABSTRACT

Lin Y-C, Tu Y-K, Chen S-C, Chen S-S, Lin I-L, Guo H-R: Comparison between botulinum toxin and corticosteroid injection in the treatment of acute and subacute tennis elbow: A prospective, randomized, double-blind, active drug-controlled pilot study. *Am J Phys Med Rehabil* 2010;89:653–659.

Objective: To compare botulinum toxin type A injection with corticosteroid injection in the treatment of tennis elbow.

Design: In this prospective, randomized, double-blind, drug-controlled trial, 19 affected elbows of 16 patients were randomly assigned to receive injection with botulinum toxin type A (Botox group) or triamcinolone acetonide (steroid group). We used the Visual Analog Scale, pain-free grip strength, and World Health Organization Quality of Life Brief Questionnaire to assess the perception of pain, grip strength, and quality of life, respectively. Measures were performed before and at 4, 8, and 12 wks after the treatment.

Results: Four weeks after the treatment, the Botox group had smaller decrease in pain ($P = 0.02$) but greater decrease in grip strength ($P = 0.01$). The difference in grip strength remained significant at 8 wks ($P = 0.03$). No significant differences in quality of life were observed throughout the study period.

Conclusions: Corticosteroid is superior to botulinum toxin type A in relieving pain in tennis elbow at 4 wks after injection. Because botulinum toxin injection did not relieve pain significantly but is associated with weakness, the muscle weakness caused by botulinum toxin is unlikely to be the sole mechanism of the pain relief observed in previous studies.

Key Words: Tennis Elbow, Humeral Lateral Epicondylitis, Botulinum Toxin Type A, Corticosteroid

Disclosures:

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Tennis elbow (humeral lateral epicondylitis) is a common painful elbow disorder that usually causes a direct influence on the performance at work and quality of life. Previous studies have reported a prevalence of 5.8% in a rural population, 7.5% in an urban population, and 14% in workers with jobs that demand repetitive wrist extension.^{1,2} The cause of tennis elbow is generally believed to be chronic overload of lateral epicondyle because of repetitive use of wrist and finger extensors, especially the extensor carpi radialis brevis (ECRB).³ The proposed treatments for tennis elbow include rest,⁴ physical therapy,⁴ oral nonsteroid anti-inflammatory drugs,⁵ local steroid injection,^{4,6} and surgical intervention,⁵ but many of them do not have sufficient scientific evidence to support their effectiveness.⁷ Steroid injection is one of the few methods proven to have short-term efficacy in treating tennis elbow.^{4,6}

Botulinum toxins are produced by the anaerobic bacteria *Clostridium botulinum* and may cause muscular paralysis by inhibiting the release of acetylcholine at neuromuscular junctions. Since the application of botulinum toxin type A in clinical use in the early 1980s, botulinum toxin injection has been safely and successfully used to treat many neurologic disorders, including dystonia and spasticity.⁸ Some clinical studies suggested that botulinum toxin type A can also be used to treat painful disorders such as migraine headache, myofascial pain syndrome, and low-back pain.⁹⁻¹² Morre et al.¹³ reported the first study on treating tennis elbow with botulinum toxin type A, which found that the treatment reduced pain in half of the 14 patients, although no side effects were observed. However, no comparison groups were included in the study. A randomized trial conducted later by Keizer et al.¹⁴ compared the effectiveness between botulinum toxin type A injection and surgery in 40 patients and found no significant difference in pain relief. Therefore, it was proposed that botulinum toxin may be able to treat the pain of tennis elbow through inducing weakness in finger and wrist extensors and thereby providing time for the rest

and repair of injured tissues.^{13,14} The results of two recent randomized, double-blind, placebo-controlled trials were inconsistent.^{15,16} Wong et al.¹⁵ observed a significant pain relief effect of botulinum toxin type A injection; however, Hayton et al.¹⁶ found that the botulinum toxin type A treatment was not superior to the placebo. Wong et al. enrolled 60 patients (11 men and 49 women) with an average age of 49 yrs and symptoms >12 mos. They used Visual Analog Scale (VAS) as the primary outcome measure and the grip strength as a secondary outcome measure. VAS and the grip strength were evaluated at baseline and at 4 and 12 wks after injection. Hayton et al. recruited 40 patients (21 men and 19 women) with an average age of 48 yrs and symptoms >6 mos. They measured the outcomes before and 3 mos after injection by VAS, grip strength, and Short Form-12 health status questionnaire.

To evaluate the efficacy of botulinum toxin type A injection in treating tennis elbow, we conducted a randomized clinical trial using corticosteroid injection as a comparison agent. This is the first study comparing botulinum toxin type A and an active agent.

METHODS

This is a prospective randomized, double-blind, drug-controlled trial to compare botulinum toxin type A injection with corticosteroid injection in treating tennis elbow. We conducted the study at the teaching hospital of a university in Taiwan, and the study protocol was approved by the institutional review board of the hospital. From December 2006 to February 2007, we recruited participants from patients suffering from upper extremity pain, who visited the outpatient orthopedic and rehabilitation departments of the hospital. Patients were examined by the same physician for the eligibility for participating in this study, and the inclusion criteria were (1) spontaneous pain over lateral epicondyle of the affected elbow; (2) local tenderness around the lateral epicondyle; and (3) pain elicited or aggravated by resisted extension of the middle digit or wrist. Exclusion criteria were (1) local steroid injection within the 3 mos before the initial evaluation; (2) trauma or history of surgical intervention, involving the lateral epicondyle of the elbow; (3) pregnancy or lactation; and (4) systemic neuromuscular or bleeding disorders. After explaining to each participant about the procedure, benefits, and potential side effects, we obtained a written informed consent. No participants received aminoglycoside antibiotics or pain-relieving medication throughout the study period.

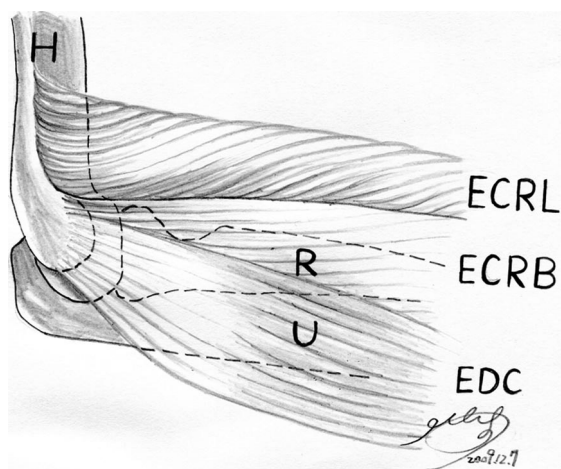


FIGURE 1. *The injection was administered into the ECRB muscle near the common origin of the wrist and finger extensors at the lateral epicondyle. H, humerus; R, radius; U, ulna; ECRL, extensor carpi radialis longus; ECRB, extensor carpi radialis brevis; EDC, extensor digitorum communis.*

The participants were allocated randomly into the Botox group (receiving injection with 1 ml 0.9% NaCl and 50 U botulinum toxin type A; Botox, Allergan) or the steroid group (receiving injection with 1 ml steroid: 40 mg triamcinolone acetonide, Squibb, Taiwan). Participants with bilateral involvement had one side assigned to the Botox group and the other side to the steroid group, and we determined the Botox group side for each participant also through a random process.

An experienced physician performed the injection for all patients, using the same technique and injection sites. The participants were blind to the medication. The test agent was injected into the ECRB muscle near common origin of wrist and finger extensors of the affected elbow using a 1-ml syringe (Becton Dickinson, Singapore) with a 27-gauge 19-mm needle (Nipro Corp., Japan). The needle was first inserted into the subcutaneous layer and then pushed further into the ECRB (Fig. 1). Localization of needle tip in the ECRB was confirmed by palpation during resisted wrist extension.

Visual analog pain scale and pain-free grip strength were the validated measures used to evaluate the effectiveness of interventions for tennis elbow.^{17,18} We used the VAS as the primary outcome measure to assess the subjective feeling of elbow pain at rest.^{15,16} Each participant was instructed to dissect a 100-mm line made of paper horizontally, with the left end indicating no pain and right end indicating the most severe pain.¹⁹ The occupational therapist measured the left por-

tion of the line by a ruler and recorded the length. We used Jamar dynamometer to measure the pain-free grip strength of hand. For each evaluation, the participant performed three repetitive tests with the elbow extended and forearm pronated, and the evaluator calculated the mean of the three measures as the final measure.^{17,18} The Taiwan Version of the WHOQOL-BREF was used to assess the participant's perception of quality of life before and after the treatment. The World Health Organization Quality of Life Brief Questionnaire-BREF is a self-administered questionnaire that assesses the quality of life in four domains: physical health domain (domain 1), psychological domain (domain 2), social relationship domain (domain 3), and environmental domain (domain 4). The Taiwanese Version has been validated and applied to previous studies,^{20,21} including some effects on the quality of life associated with pain.²¹ An occupational therapist who was blinded to the administered agent evaluated all the participants. These outcome measures were assessed at four time points: before the injection (baseline) and 4, 8, and 12 wks after the injection.

We used the SAS package for all statistical analyses. All statistical tests were performed at a two-sided significance level of 0.05. To evaluate the differences between the Botox and steroid groups, we used Fisher's exact test for categorical variables and the Wilcoxon's rank-sum test for continuous variables.

RESULTS

Twenty-six patients with upper extremity pain were initially screened. Six persons did not meet the inclusion criteria, and four qualified participants denied participation. We enrolled 16 patients with 19 affected elbows in this study. One patient who did not join the posttreatment evaluations was excluded from the statistical analysis. As a result of randomization, there were no significant differences in the two groups in terms of age, gender, occupation, affected side, and duration of symptoms (Table 1). The mean VAS score was 45.0 in the Botox group and 57.4 in the steroid group. The mean grip strength was 27.5 kg in the Botox group and 35.2 kg in the steroid group. The differences were not statistically significant. Similarly, differences in scores for the four domains of World Health Organization Quality of Life Brief Questionnaire-BREF were not statistically significant, indicating the success of randomization (Table 1).

Four weeks after treatment, both groups reported decreased pain with a significantly greater reduction in pain reported by the steroid group (-5.9 vs. -31.8 , $P = 0.02$) (Table 2). Pain remained diminished for both groups at 8 and 12

TABLE 1 Baseline characteristics of participants in the Botox and steroid groups

Characteristic	Botox Group (n = 8)	Steroid Group (n = 9)	P ^a
Gender, n			
Men	3	6	0.35
Women	5	3	
Affected side, n			
Left	5	4	0.64
Right	3	5	
Symptoms, n			
>3 mos	0	1	>0.99
<3 mos	8	8	
Occupation, n			
Nonforceful manual work	5	4	0.64
Forceful manual work	3	5	
Age (yrs), mean (SD)	45.9 (7.8)	44.6 (11.0)	0.53
VAS (mm), mean (SD)	45.0 (27.3)	57.4 (18.7)	0.27
Grip strength (kg), mean (SD)	27.5 (9.4)	35.2 (13.8)	0.21
WB-D1, mean (SD)	13.6 (2.0)	12.9 (1.7)	0.37
WB-D2, mean (SD)	13.1 (1.9)	12.6 (1.6)	0.48
WB-D3, mean (SD)	14.0 (1.4)	14.3 (1.5)	0.62
WB-D4, mean (SD)	13.1 (1.8)	13.2 (2.5)	0.92

Data are number or mean (SD).

^aP for Fisher's exact test or Wilcoxon's rank-sum test.

WB-D1, WB-D2, WB-D3, WB-D4: World Health Organization Quality of Life Brief Questionnaire domain 1, domain 2, domain 3, and domain 4; VAS, Visual Analogue Scale.

wks, but the differences in pain ratings between groups at 8 and 12 wks were not significant. Interestingly, the Botox group exhibited a trend toward diminished pain ratings as time progressed, whereas the steroid group reported less reduction as time progressed, but the differences were not statistically significant. A small decrease in grip strength was observed in the Botox group at 4 wks, and this decrease was less evident at 8 and 12 wks. A small increase in grip strength was observed in the steroid group. The differences in grip strength were considered significant at 4 and 8 wks. No statistically significant differences were observed between the groups with respect to quality of life at 4, 8, and 12 wks.

There was no severe side effects in the participants. In the Botox group, mild weakness in wrist extension and middle digit extension were noted in all patients at 4 and 8 wks after the treatment. They did not interfere with the activities of daily living, and the weakness recovered completely in all patients at 12-wk follow-up. Such a phenomenon was not observed in the steroid group.

TABLE 2 Differences in the changes in measurements of the Visual Analogue Scale (VAS), grip strength, and World Health Organization Quality of Life Brief Questionnaire between the Botox and steroid groups after the treatment

	Botox Group	Steroid Group	P ^a
Four weeks after the treatment			
VAS	-5.9 ± 28.4	-31.8 ± 22.1	0.02 ^b
Grip strength (kg)	-7.5 ± 5.5	1.9 ± 6.8	0.01 ^b
WB-D1	-0.5 ± 1.9	0.7 ± 1.3	0.22
WB-D2	-0.3 ± 2.8	0.8 ± 2.2	0.38
WB-D3	-0.5 ± 1.4	0.6 ± 1.0	0.15
WB-D4	0.5 ± 1.8	0.8 ± 1.6	0.52
Eight weeks after the treatment			
VAS	-9.6 ± 22.5	-16.7 ± 27.5	0.54
Grip strength (kg)	-5.7 ± 4.8	0.9 ± 5.3	0.03 ^b
WB-D1	-0.4 ± 1.6	-0.1 ± 1.6	0.67
WB-D2	0.0 ± 1.3	0.2 ± 2.1	0.67
WB-D3	0.0 ± 1.4	0.7 ± 1.4	0.28
WB-D4	0.5 ± 1.4	1.1 ± 1.3	0.37
Twelve weeks after the treatment			
VAS	-11.4 ± 28.5	-14.4 ± 27.0	0.74
Grip strength (kg)	-3.4 ± 5.2	0.7 ± 5.5	0.06
WB-D1	0.0 ± 1.9	0.2 ± 1.3	0.61
WB-D2	0.5 ± 1.6	0.8 ± 2.1	0.74
WB-D3	0.8 ± 1.5	0.7 ± 0.9	0.89
WB-D4	1.0 ± 1.7	0.9 ± 1.7	0.89

Data are mean ± SD.

^aP for the Wilcoxon's rank-sum test.

^bP < 0.05.

WB-D1, WB-D2, WB-D3, WB-D4: World Health Organization quality of life brief questionnaire domain 1, domain 2, domain 3, and domain 4.

DISCUSSION

Previous studies have demonstrated the short-term effectiveness of steroid injection in treating tennis elbow.⁴⁻⁷ Steroid injection is an effective treatment option in the short term for patients with tennis elbow, as revealed by randomized controlled trials with the comparisons of observation only, physical therapy alone, and steroid injection alone.^{4,6} Some previous studies found that botulinum toxins type A injection was effective in treating tennis elbow.^{13,14} However, the results of randomized, double-blind, placebo-controlled trials were not consistent.^{15,16} However, we could not find any previous studies comparing botulinum

toxin type A and steroid injection in treating tennis elbow.

In this study, we concluded that patients receiving corticosteroid injection experienced greater pain relief at 4 wks but not at 8 or 12 wks. The duration of short-term pain relief by corticosteroid is similar to the effect reported in the previous randomized controlled trials and systemic review articles.^{4,6,7}

It has been proposed that botulinum toxin type A injection into the extensors of wrist and fingers can cause temporary muscle weakness and thus might facilitate the autorepair mechanism in tennis elbow. We found that grip strength of the affected hands decreased at 4 and 8 wks after the botulinum toxin treatment but not at 12 wks. This is compatible with the previous finding that the effect of botulinum toxin type A injection disappeared 3 mos later because of the resprouting of peripheral nerve.²² We observed weakness of extensors of the wrist and middle digit in all the participants in the Botox group, and this indicated that the dose was high enough and the injection site was precise enough to cause weakness of muscles. There was no significant pain relieving effect after botulinum toxin injection in our study. The mechanism of action for botulinum toxin in the treatment of tennis elbow may be not only through the mechanism of rest and repair. There are some studies supporting the direct analgesia effect of botulinum toxin.^{23–25} Ishikawa et al.²³ found botulinum toxin type A that can inhibit the production of substance P in rabbit iris muscles, and Welch et al.²⁴ had similar findings in dorsal root ganglion of rat embryo. Furthermore, pretreatment with subcutaneous botulinum toxin type A injection can reduce the formalin-induced pain reaction in rats, and it is believed that this effect is caused by the inhibition of the release of pain-related neurotransmitters because no muscular weakness was noted at the dosage used.²⁵ Botulinum toxins can suppress the release of nociception-related neuropeptides such as substance P and calcitonin gene-related peptide.²⁶ Inhibition of cytokines and neuropeptides in the enthesis of tendon may account for the mechanism of botulinum toxin type A in treating tennis elbow.²⁷

Hayton et al.¹⁶ conducted the first randomized, double-blind, placebo-controlled trial in 40 patients with tennis elbow and concluded that the injection of 50 U Botox was not superior to the injection of saline in pain relief. Wong et al.¹⁵ injected 60 U of Dysport (Beaufour Ipsen International, Maidenhead, United Kingdom), another product of botulinum toxin type A, and found that patients in the Dysport group had significant reduction in VAS for pain without significant loss of grip strength at 4 and 12 wks after the treatment. Wong et al. thought that the pain-relieving effect of botulinum toxin for

tennis elbow may be due to the direct analgesia instead of auto repair after weakness and resting.^{15,28} Similarly, in a randomized, double-blind, placebo-controlled trial published after we had initiated this study, Placzek et al.²⁹ injected 60 U of Dysport into the painful origin of forearm extensor muscles and found that botulinum toxin injection could lead to pain relief for 18 wks in the treatment of chronic tennis elbow.

Among the three previous randomized controlled (all used placebos) trials on the treatment of tennis elbow using botulinum toxin, the major differences were the dosage and injection sites.^{15,16,29} The studies by Wong et al.¹⁵ and Placzek et al.²⁹ administered 60 U of Dysport to the painful site, and a significant pain-relieving effect was observed in both studies. Therefore, results of the two studies were consistent. Hayton et al.¹⁶ used 50 U Botox for the intramuscular injection at 5 cm distal to the maximum point of tenderness instead of the tender point itself and did not observe a significant pain-relieving effect. We injected the same dosage of botulinum toxin (Botox 50 U) that administered by Hayton et al. to the ECRB muscle near common origin of wrist and finger extensors instead of the tender point and failed to observe a significant pain-relieving effect. Therefore, our study results are consistent with those from the study by Hayton et al. Using an assumed potential ratio of 1:3 (Dysport: Botox), we estimated that the dosage used by Wong et al. and Placzek et al. is equivalent to 40% of the dosage used in our study and Hayton et al. (Botox 50 U $\times$ 40% = Dysport 60 U).^{15,16,29}

It is interesting to note that the trials with smaller doses of botulinum toxin type A injected into the painful site led to significant reduction in tennis elbow pain without causing grip strength weakness, whereas larger doses of botulinum toxin type A injected into the muscle decreased strength but did not improve pain in the patients with tennis elbow. Because muscle weakness was successfully induced in our study, our findings do not support the theory that the pain-relieving effect of botulinum toxin for tennis elbow is through the mechanism of autorepair of tissues after muscle weakness and resting.^{13,14} Taking the results of all four studies into account, we conclude that the pain relief caused by botulinum toxin injection observed by other investigators^{13–15,29} was more likely to be due to the other mechanisms such as a direct analgesic effect.

In our double-blind study, the same experienced physician performed the injection for all participants. The ECRB muscle targeted for drug administration seemed to be injected correctly, as confirmed by the evidence that all patients in the Botox group had weakness, and therefore, these patients may eventually suspect they had received

Botox injection. This effect may cause this trial to be an imperfect double-blind study.

There are some limitations in generalizing our study results. Only one of our participants had symptoms of tennis elbow lasting for >3 mos, and therefore, there are uncertainties in applying the results to patients with longer durations of symptoms. The World Health Organization Quality of Life Brief Questionnaire-BERF scores revealed no significant changes in both groups in our study, although there was significant short-term pain-relieving effect in the steroid group. Therefore, there are also uncertainties in applying the results to patients with symptoms that are severe enough to affect the quality of life.

CONCLUSION

This study compares the effect between botulinum toxin and corticosteroid injection into ECRB muscle near common origin of wrist and finger extensors. The steroid group experienced greater pain relief at 4 wks but not at 8 or 12 wks. The Botulinum group demonstrates a small reduction in grip strength, which was considered significant at 4 and 8 wks. Therefore, it does not seem that reduction in strength is the mechanism for pain relief as suggested by other authors.

Steroid injection may be a better option for acute, short-term pain relief or as a facilitator for more comprehensive rehabilitation in patients with symptoms of <3 mos duration.

The site of injection and the dosage of botulinum toxin may influence the results, and therefore, further studies should be conducted using different dosage and injection sites. In particular, a clinical trial comparing effects of botulinum toxin and corticosteroid injection at the tender point could help to better determine the mechanism for the inconsistently reported pain-relieving effect of botulinum toxin type A in treating some musculoskeletal conditions.

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