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Botulinum Toxin Injection in the Treatment of Tennis Elbow

A DOUBLE-BLIND, RANDOMIZED, CONTROLLED, PILOT STUDY

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Investigation performed at Wrightington Hospital, Wigan, and Royal Liverpool University Hospital, Liverpool, United Kingdom

Background: A recent report has suggested that local injection of botulinum toxin type A is an effective method of treatment for chronic tennis elbow. The toxin is thought to provide temporary paralysis of the painful common extensor origin, thereby allowing a healing response to occur. To test this theory, we performed a double-blind, randomized, controlled, pilot trial comparing injections of botulinum toxin type A with those of a placebo (normal saline solution) in the treatment of chronic tennis elbow.

Methods: Forty patients with a history of chronic tennis elbow for which all conservative treatment measures, including steroid injection, had failed were randomized into two groups. Half the patients received 50 units of botulinum toxin type A, and the remainder received normal saline solution. The intramuscular injections were performed 5 cm distal to the maximum point of tenderness at the lateral epicondyle, in line with the middle of the wrist. The two solutions used for the injections were identical in appearance and temperature. The results of a quality-of-life assessment with the Short Form-12 (SF-12), the pain score on a visual analogue scale, and the grip strength measured with a validated Jamar dynamometer were recorded before and three months after the injection.

Results: Three months following the injections, there was no significant difference between the two groups with regard to grip strength, pain, or quality of life.

Conclusions: With the numbers studied, we failed to find a significant difference between the two groups; thus, we have no evidence of a benefit from botulinum toxin injection in the treatment of chronic tennis elbow.

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

Tennis elbow, or lateral humeral epicondylitis, is a common condition. The term epicondylitis suggests inflammation, although histological analysis of the involved tissue invariably fails to show inflammation. The majority of cases resolve with conservative methods, including rest and splints. A local injection of corticosteroids into the painful area is the most common method of nonoperative treatment; however, there is a lack of evidence demonstrating that corticosteroid injections have a benefit over simple anti-inflammatory agents. In addition, corticosteroid injections are not without complications and may cause lipodystrophy.

Recent reports comparing botulinum toxin type A with surgery suggested that injection of botulinum toxin is an effective treatment for resistant tennis elbow. Botulinum toxin binds to specific receptors at the presynaptic cholinergic end plate membrane and blocks acetylcholine release. Therefore, for the treatment of tennis elbow, an injection is given to provide temporary paralysis of the affected muscle, thereby removing the tensile forces acting on the extensor origin. These effects are reversible after three to four months, which may provide adequate time for tissue-healing of the Nirschl lesion at the lateral epicondyle. Botulinum toxin type A has many clinical applications, including the treatment of strabismus, blepharospasm, and other hyperkinetic movement disorders. More recently, botulinum toxin has been used successfully to treat focal hyperhidrosis.

The studies of tennis elbow noted above were not placebo-controlled trials, which are needed in order to evaluate the true efficacy of a treatment. We performed a randomized, controlled, pilot trial to investigate the effects of botulinum toxin type A in the treatment of chronic tennis elbow (of more than six months’ duration) for which all conservative treatment measures, including physiotherapy and steroid injection, had failed. Our null hypothesis was that there is no difference between botulinum toxin type A and a placebo in the treatment of chronic tennis elbow.

Materials and Methods

Prior to patient participation, the study was approved by the ethical committees of both hospitals involved in the
study. Forty consenting patients with chronic tennis elbow were recruited to participate. All patients had had clinically diagnosed tennis elbow for more than six months, and all had received at least one corticosteroid injection and a full course of physiotherapy. Tennis elbow was diagnosed clinically on the basis of well-localized pain over the lateral epicondyle and increased pain at this site on resisted wrist extension. All patients had a full range of movement with normal anatomical alignment of the elbow. Patients were excluded if they had any neck symptoms, previous elbow surgery, systemic disease, or a negative provocation test for tennis elbow.

The patients were block randomized into two groups. One group was to receive an injection of 50 units of botulinum toxin type A reconstituted in 2 mL of normal saline solution (Allergan, Irvine, California), and the other was to receive a placebo injection of 2 mL of normal saline solution only. Block randomization is a method used to prevent unequal treatment-group sizes, since it ensures that at certain points the numbers of participants in each group are equal. For example, a sample of forty patients in a trial is split into ten groups of four patients. Each subset of four patients is then randomized, with two patients assigned to the treatment group and two assigned to the control group. This process is repeated as the trial progresses. Therefore, if the trial is stopped prematurely, the numbers of patients in each group will be approximately equal. Fifty units was selected as the strength of botulinum toxin type A to be consistent with the strength used in the only previous studies of this kind to show an apparent therapeutic effect6,7. The solutions were drawn up independently, and the injection was performed by a physician who was blinded to its content. Both injection solutions were colorless and of equal temperature to maintain blinding. The injection was administered 5 cm distal to the area of maximal tenderness at the lateral epicondyle, in line with the middle of the wrist, with a 21-gauge needle inserted deep to the forearm fascia (Fig. 1).

Prior to the injection, patients completed the Short Form-12 (SF-12) health status questionnaire13. Pain was assessed on a linear visual analogue scale14 ranging between 0 and 10, with 0 representing no pain and 10 representing the worst pain imaginable. Grip strength was recorded, in kilograms, as an average of three readings with a validated Jamar dynamometer on both the affected and unaffected sides. The patients were contacted by telephone at one week to ensure that no adverse reactions had occurred from the injection. The patients were examined in our clinic three months after the injection, and the same data as had been obtained before the injection were recorded. No adjunctive treatment, such as physiotherapy, was prescribed during the three-month period. Statistical analysis was performed with p < 0.05 as the level of significance.

Results

Of the forty patients who were recruited, nineteen were randomized to receive botulinum toxin type A and twenty-one were randomized to receive a placebo injection. Eighteen patients in the botulinum toxin group completed the study, whereas one patient had an operation, performed by a different clinician, before the three-month follow-up period was completed. Nineteen patients in the placebo group com-
completed the study, whereas one patient had an operation before the completion of the three-month follow-up period and one failed to return for follow-up. The mean age of the patients was forty-eight years (range, thirty-five to seventy-one years). There were twenty-one men and nineteen women.

An extensor lag was recorded when the patient was unable to fully extend a digit actively. Twelve of the eighteen patients in the botulinum toxin group had a transient 2-cm extensor lag of the long finger that was noticeable at one week. All extensor lags disappeared by three months after the injection. Two patients, one of whom repaired watches and the other of whom worked as a typist and also played the guitar, reported that the extensor lag caused functional problems.

**Grip Strength** (Table I)
Prior to the injection, there was no significant difference in the mean grip strength of the affected limb between the botulinum toxin group (mean, 27.6 kg) and the placebo group (mean, 30.9 kg) (p = 0.46). At three months after the injection, there was also no significant difference between the groups with regard to the mean grip strength (p = 0.90), the absolute change in the mean grip strength compared with the preinjection level (p = 0.20), or the percentage change in the mean grip strength (p = 0.08).

There was no significant difference in the mean grip strength of the unaffected limb between the botulinum toxin group (mean, 34.6 kg) and the placebo group (mean, 36.8 kg) prior to the injection (p = 0.56). At three months after the injection, there was also no significant difference between the groups with regard to the mean grip strength (p = 0.83), the mean absolute change in grip strength (p = 0.49), or the mean percentage change in grip strength (p = 0.56).

**Pain Assessed on the Visual Analogue Scale** (Table II)
Prior to the injection, there was no significant difference in the mean score on the visual analogue scale between the botulinum toxin group (mean, 8.80 cm) and the placebo group (mean, 9.43 cm) (p = 0.67). At three months after the injection, there was also no significant difference between the groups with regard to the mean score (p = 0.54), the mean absolute change in score (p = 0.49), or the mean percentage change in score (p = 0.80).

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**TABLE I Grip Strength as Measured with the Jamar Dynamometer**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Grip Strength (Botulinum Toxin/Placebo)</th>
<th>Difference in Grip Strength Between Groups</th>
<th>95% Confidence Intervals</th>
<th>P Value</th>
<th>Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinjection</td>
<td>27.6/30.9 kg</td>
<td>3.26 kg</td>
<td>−12.1 5.59</td>
<td>0.46</td>
<td>190</td>
</tr>
<tr>
<td>Postinjection</td>
<td>30.4/30.9 kg</td>
<td>0.57 kg</td>
<td>−9.53 8.39</td>
<td>0.90</td>
<td>186</td>
</tr>
<tr>
<td>Absolute change*</td>
<td>−</td>
<td>2.69 kg</td>
<td>−1.45 6.84</td>
<td>0.20</td>
<td>41†</td>
</tr>
<tr>
<td>% change*</td>
<td>−</td>
<td>16.67%</td>
<td>−2.31 35.64</td>
<td>0.08</td>
<td>854</td>
</tr>
<tr>
<td>Unaffected side</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinjection</td>
<td>34.6/36.8 kg</td>
<td>2.19 kg</td>
<td>−9.78 5.4</td>
<td>0.56</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Postinjection</td>
<td>36.1/36.7 kg</td>
<td>0.91 kg</td>
<td>−9.32 7.49</td>
<td>0.83</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Absolute change*</td>
<td>−</td>
<td>1.28 kg</td>
<td>−2.44 5</td>
<td>0.49</td>
<td>Not calculated</td>
</tr>
<tr>
<td>% change*</td>
<td>−</td>
<td>3.41%</td>
<td>−8.45 15.26</td>
<td>0.56</td>
<td>Not calculated</td>
</tr>
</tbody>
</table>

*Between preinjection and postinjection values. †The estimate used for subsequent power analysis.

---

**TABLE II Pain as Assessed with a Visual Analogue Scale**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Pain Score (Botulinum Toxin/Placebo)</th>
<th>Difference in Score Between Groups</th>
<th>95% Confidence Intervals</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinjection</td>
<td>8.80/9.43 cm</td>
<td>0.63 cm</td>
<td>−3.61 2.36</td>
<td>0.67</td>
</tr>
<tr>
<td>Postinjection</td>
<td>11.35/12.46 cm</td>
<td>1.1 cm</td>
<td>−4.71 2.49</td>
<td>0.54</td>
</tr>
<tr>
<td>% change*</td>
<td>−</td>
<td>8.99%</td>
<td>−80.72 62.74</td>
<td>0.80</td>
</tr>
<tr>
<td>% fraction change*</td>
<td>−</td>
<td>2.41%</td>
<td>−22.1 17.28</td>
<td>0.81</td>
</tr>
<tr>
<td>Absolute change*</td>
<td>−</td>
<td>0.483 cm</td>
<td>−4.42 3.45</td>
<td>0.81</td>
</tr>
</tbody>
</table>

*Between preinjection and postinjection values.
tage fraction change in the score (p = 0.81), or the mean change in the absolute score in centimeters (p = 0.81).

**Quality of Life Measured with the SF-12 (Table III)**

Prior to the injection, there was no significant difference in the mean physical function SF-12 score between the botulinum toxin group (mean, 35.70 points) and the placebo group (mean, 41.08 points), although the difference approached significance (p = 0.06). At three months after the injection, there was also no significant difference in the mean physical function score between the botulinum toxin group (mean, 46.84 points) and the placebo group (mean, 50.69 points) (p = 0.16), between the mean percentage change in the physical function score (p = 0.84), or between the mean absolute change in the physical function score (p = 0.83).

There was no significant difference in the mean mental function SF-12 score between the botulinum toxin group (mean, 46.84 points) and the placebo group (mean, 50.69 points) prior to the injection (p = 0.30). At three months after the injection, there was also no significant difference in the mean mental function score between the botulinum toxin group (mean, 44.61 points) and the placebo group (mean, 48.87 points) (p = 0.42) or in the mean percentage change (p = 0.80) or absolute change (p = 0.93) in the mental function score.

**Discussion**

Recent reports have suggested that botulinum toxin type A may be as effective as surgery in the treatment of chronic tennis elbow. However, as surgery is required in only a minority of patients, botulinum toxin treatment needs to be assessed as a treatment regimen on its own. With this in mind, we investigated the effects of injection of botulinum toxin type A on tennis elbow in a double-blind, placebo-controlled trial. We concluded that it was not clinically effective, and therefore we accepted our null hypothesis.

Twelve of the eighteen patients who received an injection of botulinum toxin type A had a transient extensor lag of the long finger. This did not cause a functional problem in the majority of these patients, but it was not tolerable to two individuals who required intricate maneuvers as part of their hobby or work. Although six of the eighteen patients did not have an extensor lag, they had subjective weakness in the extensor mechanism, possibly as a result of the injection temporarily paralyzing the muscle. Keizer et al. looked for evidence of an extensor lag in their twenty patients to confirm that the injection had been located correctly, and they repeated the injection in eight patients who did not have a finger drop. Six of our patients did not demonstrate a finger drop, which perhaps suggests that the injection was not in the correct position; however, reanalysis of our results showed no difference between the groups with and without a finger drop with regard to any of the assessed outcome measures. The presence of an extensor lag did not compromise the blinding of the study. The patients completed marking the visual analogue scale and filling out the SF-12 form before they were examined by the blinded assessor, and the patients picked up the Jamar dynamometer before the blinded assessor observed them so that the assessor would not be able to detect an extensor lag.

The patients treated with the botulinum toxin had an average 10% improvement in grip strength on the affected side, whereas the preoperative and postoperative mean grip strengths were the same in those treated with the placebo; however, this difference did not reach significance (p = 0.08; 95% confidence interval, −2.31 to 35.64). No substantial difference in the grip strength on the unaffected side was seen between the groups, with a 4% improvement in the botulinum toxin group and a 1% improvement in the placebo group. Both groups also showed similar improvements in the scores for pain and quality of life. However, because there was a nearly significant difference between groups with regard to the percentage change in grip strength on the affected side (p = 0.08), one must question the number of patients recruited in the study. In order to show an assumed clinically relevant
difference of 2 kg, with an 80% power and a type-I error of 5%, 300 patients would be needed (150 in each treatment group). If a subsequent study were to be planned, it would be advisable to use the mean change in grip strength as a primary variable because the variability for this parameter was lowest in the present study and it came close to identifying a significant difference between groups (p = 0.196). In addition, grip strength is a quantifiable measurement of effect, unlike the more subjective measurement of pain.

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