Is lateral epicondylitis a new indication for botulinum toxin?

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Lateral epicondylitis, or tennis elbow, is a prevalent and costly disorder that affects 1%–3% of the general population[1] and up to 15% of at-risk workers.[2] There is limited evidence for the effectiveness of current approaches to treatment, and optimal evidence-based treatment is unclear.[3] Although recent studies report that 90% of patients in primary care improve or recover completely after one year,[4] lateral epicondylitis results in substantial disability, use of health care resources, loss of productivity and high costs. New, more effective therapies that shorten the duration of symptoms have the potential to be of substantial value.

Espandar and colleagues present the results of a randomized placebo-controlled trial that investigated the efficacy and safety of botulinum toxin type A for the management of lateral epicondylitis in 48 patients.[5] Botulinum toxin A, a neurotoxin, irreversibly blocks the presynaptic release of acetylcholine at the neuromuscular junction, which results in paralysis of the muscles.

Lateral epicondylitis is thought to be an overload injury involving the common extensor muscles at the lateral epicondyle. Therefore, it has been proposed that temporary paralysis of the proximal extensor muscles of the forearm will aid recovery.[5] Botulinum toxin is also thought to have some analgesic properties.[6]

Three other randomized placebo-controlled trials of botulinum toxin for the management of lateral epicondylitis have had conflicting results.[7–9] In one trial, the treatment reduced the pain, but it had no effect on grip strength at 4 and 12 weeks.[8] The second trial found a substantial reduction in pain, and improvement in the patients' and physicians' global assessment of treatment at 6 and 18 weeks; however, there was no difference between the treatment and control groups with respect to maximum pain or grip strength.[9] A smaller, third study involving 40 patients found no substantial differences between the treatment and control groups in pain, grip strength or quality of life 12 weeks after treatment.[7]

Consistent with the results of two of these trials, Espandar and colleagues found significant reductions in pain at rest 4, 8 and 16 weeks after treatment with botulinum toxin.[5] They also found that the intensity of pain during maximum pinch decreased at all time points in the treatment group; however, there was no significant difference in pain during maximum grip or in grip strength at any point between the two groups.

One of the problems in trying to draw conclusions from available trials about the efficacy of botulinum toxin is the heterogeneous nature of the protocols used for the active intervention. Dosage, preparation of the toxin, the site of needle insertion and the method of injection have all varied. Espandar and colleagues suggest that injection at a fixed distance from an anatomic landmark could result in inadequate paralysis of the intended muscle, which could explain differences in observed efficacy.[5] The authors marked the injection site at a distance one-third the length of the patient's forearm from the tip of the lateral epicondyle along the course of the posterior interosseous nerve to ensure paralysis of the extensor digitorum muscle, which is proposed to have an important role in the development of lateral epicondylitis.[5] In contrast to the results of trials that reported rates of paresis between 20% and 66% in the extensor muscles of the third and fourth fingers,[7,8] Espandar and colleagues reported an impressive rate of 96%, and the paresis lasted up to 16 weeks in most patients.[5]

However, as the authors point out, the high rate of paresis in the treatment group, although it indicated the success rate of the paralysis, was also a major limitation of the trial because it could not ensure blinding of the participants and assessors.[5] Furthermore, the expected paresis in the extensor muscles of the third and fourth fingers may make this treatment unsuitable for many people.

Drawing conclusions from available trials is also hampered by the timing of, and variation in, outcome measures.

Key points

- Injection of botulinum toxin type A is a promising new treatment for lateral epicondylitis, although some doubt remains about its true efficacy.
- Further study is required to determine the most important outcomes from the patient's perspective and how these should be assessed.
- The development of a standardized set of outcome measures that consider function and quality of life would substantially advance efforts to determine the optimal treatment of lateral epicondylitis.

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For example, only one trial specified which follow-up period should be considered,[9] and differences in how the question of pain is framed are likely to yield different responses. As well as measuring continuous and maximum pain over the previous 48 hours, Placzek and colleagues used a composite measure comprising pain associated with four isometric or passive movements and localized tenderness at the lateral epicondyle.[9] Espandar and colleagues measured primarily pain at rest, but they also included levels of pain during maximum grip or maximum pinch.[5] They suggest that pain with activity might be of equal or more importance than pain at rest to some patients.

None of the trials reported a beneficial effect of botulinum toxin on grip strength; however, although not explicitly stated, all four trials appeared to have measured maximum, rather than pain-free, grip strength.[5,7–9] Previous studies have found pain-free grip strength to be a more valid outcome measure and more strongly associated with functional and working disability.[10] Espandar and colleagues propose that grip strength, which was transiently reduced in the treatment group, may not be a valid outcome measure for studying the effects of botulinum toxin because of the confounding effect of paralysis of the extensor muscles.[5]

Several other new interventions — including transdermal glyceryl trinitrate patches, sclerosing injections, injection of platelet-rich plasma or autologous blood, and injection of laboratory-prepared, collagen-producing cells derived from dermal fibroblasts — have been proposed for treating lateral epicondylitis because they may stimulate healing.[11–13] None has been proven to be efficacious in well-designed, randomized controlled trials. Because of the favourable natural history of lateral epicondylitis and the fact that the primary relevant outcome for patients is symptom relief, randomized controlled trials in which the participants are blinded to treatment allocation are the only valid way to establish the efficacy of treatment strategies for this condition.

The high costs to individuals and society related to sick leave and disability resulting from lateral epicondylitis show a clear need to identify the most cost-effective therapies for this disorder. Injection with botulinum toxin has been shown in most trials to reduce pain significantly when compared with placebo. However, it has not been shown to reduce pain during maximum grip or to improve maximum grip strength, and its effect on function, quality of life and pain-free grip strength is unknown. The temporary partial or complete paresis of the extensor muscles of the third and fourth fingers may be unacceptable for some people, and it is not clear whether any therapeutic effects remain or diminish once the muscle paralysis has abated. Future studies should be directed toward reliable delivery of a standardized dose of botulinum toxin that will achieve adequate muscle paralysis without appreciably impairing hand function.

Further research is needed to determine the most relevant and important outcome measures of lateral epicondylitis from the patient's perspective, and how these should be assessed. Development of a standardized set of outcome measures that consider function and quality of life would substantially advance efforts to determine the optimal treatment of lateral epicondylitis.

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REFERENCES

1. Walker-Bone K, Palmer K, Reading I, et al. Prevalence and impact of musculoskeletal disorders of the upper limb in the general population. *Arthritis Rheum* 2004;51:642-51.
2. Fan ZJ, Silverstein BA, Bao S, et al. Quantitative exposure-response relations between physical workload and prevalence of lateral epicondylitis in a working population. *Am J Ind Med* 2009;52:479-90.
3. Johnson GW, Cadwallader K, Scheffel SB, et al. Treatment of lateral epicondylitis. *Am Fam Physician* 2007;76:843-8.
4. Smidt N, Lewis M, Van Der Windt DAWM, et al. Lateral epicondylitis in general practice: course and prognostic indicators of outcome. *J Rheumatol* 2006;33:2053-9.
5. Espandar R, Heidari P, Rasouli MR, et al. Use of anatomic measurement to guide injection of botulinum toxin for the management of chronic lateral epicondylitis: a randomized controlled trial. *CMAJ* 2010;182:768-73.
6. Mense S. Neurobiological basis for the use of botulinum toxin in pain therapy. *J Neurol* 2004;251(Suppl 1):1-7.
7. Hayton MJ, Santini AJ, Hughes PJ, et al. Botulinum toxin injection in the treatment of tennis elbow. A double-blind, randomized, controlled, pilot study. *J Bone Joint Surg Am* 2005;87:503-7.
8. Wong SM, Hui AC, Tong PY, et al. Treatment of lateral epicondylitis with botulinum toxin: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2005;143:793-7.
9. Placzek R, Drescher W, Deuretzbacher G, et al. Treatment of chronic radial epicondylitis with botulinum toxin A. A double-blind, placebo-controlled, randomized multicenter study. *J Bone Joint Surg Am* 2007;89:255-60.
10. Smidt N, van der Windt DA, Assendelft WJ, et al. Interobserver reproducibility of the assessment of severity of complaints, grip strength, and pressure pain threshold in patients with lateral epicondylitis. *Arch Phys Med Rehabil* 2002;83:1145-50.
11. Paoloni JA, Murrell GAC, Burch RM, et al. Randomised, double-blind, placebo-controlled clinical trial of a new topical glyceryl trinitrate patch for chronic lateral epicondylosis. *Br J Sports Med* 2009;43:299-302.
12. Rabago D, Best TM, Zgierska AE, et al. A systematic review of four injection therapies for lateral epicondylosis: prolotherapy, polidocanol, whole blood and platelet-rich plasma. *Br J Sports Med* 2009;43:471-81.
13. Connell D, Datir A, Alyas F, et al. Treatment of lateral epicondylitis using skin-derived tenocyte-like cells. *Br J Sports Med* 2009;43:293-8.

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