What is the clinical effectiveness and cost-effectiveness of conservative interventions for tendinopathy? An overview of systematic reviews of clinical effectiveness and systematic review of economic evaluations

Linda Long, Simon Briscoe, Chris Cooper, Chris Hyde and Louise Crathorne*

Peninsula Technology Assessment Group (PenTAG), Evidence Synthesis and Modelling for Health Improvement (ESMI), University of Exeter Medical School, Exeter, UK

*Corresponding author

Declared competing interests of authors: none

Published January 2015
DOI: 10.3310/hta19080

Scientific summary

Effectiveness of interventions for tendinopathy

Health Technology Assessment 2015; Vol. 19: No. 8
DOI: 10.3310/hta19080

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Lateral elbow tendinopathy (LET) is associated with pain over the lateral epicondyle associated with gripping and manipulation of the hand. Pain in this area is also referred to as 'tennis elbow', 'lateral elbow pain', 'lateral epicondylitis', 'lateral epicondylalgia', 'rowing elbow', 'tendonitis of the common extensor origin' and 'peritendinitis of the elbow'. The condition is referred to throughout this report as 'lateral elbow tendinopathy'. It is a common complaint causing characteristic pain in the lateral elbow and upper forearm, and tenderness of the forearm extensor muscles. It is thought to be an overuse injury, caused by repetitive loading of the extensor tendons of the forearm where they attach to the lateral epicondyle. LET can have a major impact on the patient's social and professional life. The clinical presentation of LET is reasonably straightforward and easy to recognise, which contrasts with a more complex underlying pathophysiology. The condition is challenging to treat and prone to recurrent episodes. The average duration of a typical episode ranges from 6 to 24 months, with most patients (89%) reporting recovery by 1 year.

The initial management of lateral epicondylitis aims to treat symptoms of pain and inflammation, promote healing, increase work and leisure activities, and reduce risk of aggravating the condition or developing a new injury. Pharmacotherapy, electrophysical therapy, exercise and multimodal therapy tend to be the main conservative management strategies for LET.

Objectives

This systematic review aims to summarise the evidence concerning the clinical effectiveness and cost-effectiveness of conservative interventions for LET by:

- providing an overview of systematic reviews of the evidence for the clinical effectiveness of conservative interventions for the treatment of LET
- quantifying the number of randomised controlled trials (RCTs) meeting the specified inclusion criteria not included in the most valid and up-to-date systematic reviews included in the overview (note that, in line with the protocol, quality appraisal of RCTs was not undertaken as part of this mapping exercise)
- identifying RCTs that could contribute further evidence to existing systematic reviews (included in the overview) and for which there may be a need for a systematic review to synthesise evidence for newer treatments
- performing a systematic review of cost-effectiveness studies.

Methods

Data sources

Electronic databases were searched from inception to January 2013. The databases searched included MEDLINE (Ovid); MEDLINE In-Process & Other Non-Indexed Citations (via Ovid); EMBASE (via Ovid); Allied and Complementary Medicine Database (via Ovid); Cumulative Index to Nursing and Allied Health Literature (via EBSCO*host*); Web of Science (via Thomson Reuters); Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials; Database of Abstracts of Reviews of Effects (via Cochrane); Health Technology Assessment (via Cochrane); Physiotherapy Evidence Database; and ClinicalTrials.gov. The NHS Economic Evaluation Database (via Cochrane) was also searched for cost-effectiveness studies. All database searching was conducted by an information specialist.

Further searching was carried out by checking the references of retrieved studies and contacting experts. The internet was also searched for background information.

Study selection

Relevant studies were identified in two stages. Titles and abstracts were examined independently by two researchers and screened for possible inclusion. Disagreements were resolved by discussion. Full texts of the identified studies were obtained and two researchers examined these independently for inclusion or exclusion, and disagreements were resolved by discussion. A third reviewer was available if necessary.

Data extraction and critical appraisal

Two reviewers (LC and LL) read the full text of relevant reviews and assessed the methodological quality of included reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) checklist. Studies scoring 8 points (out of a possible 11) or higher were then analysed using a Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Data were extracted by LL and checked by CH. Disagreements were resolved by discussion.

Results

Number and quality of effectiveness studies

From the 1029 unique titles and abstracts screened, 29 systematic reviews were identified which matched our inclusion criteria that had been published since 2003. The 29 reviews were quality appraised using the AMSTAR checklist; five were considered high quality and analysed using the GRADE approach. A total of 36 RCTs were identified that were not included in a systematic review and 29 RCTs were identified that had only been evaluated in an included systematic review of intermediate/low quality. These were then mapped to existing systematic reviews for which further evidence could provide updates.

Summary of effectiveness results

- There was insufficient evidence to demonstrate either benefit or lack of effect of extracorporeal shock wave therapy (ESWT) for LET. An updated systematic review is required, although given the small sample sizes of the subsequently identified RCTs (< 100), we suggest that further larger-scale, good-quality RCTs should be considered.
- There was insufficient evidence to demonstrate either benefit or lack of effect of laser therapy for LET. An updated systematic review is required; however, we also recommend that some consideration is also given to conducting larger-scale RCTs.
- There was low-level evidence for beneficial pain relief in the short and intermediate term using therapeutic ultrasound (and friction massage) for LET. An updated systematic review is required.
- There was insufficient evidence to demonstrate either benefit or lack of effect of exercises for LET. An updated systematic review is required; however, only three subsequent RCTs were identified and they have small sample sizes. Therefore, we suggest that consideration is given to conducting larger-scale, good-quality RCTs using a core set of outcome measures and appropriate follow-up periods.
- There was low-level evidence for beneficial pain relief and increased functionality in the short term using glucocorticoid injections (GCIs) for LET, with no benefits reported for the intermediate and long term. An updated systematic review is required. We also recommend (1) conducting large-scale, good-quality RCTs with sufficient sample size and the inclusion of core outcome measures to investigate the longer-term effects of GCIs, and (2) a subgroup analysis of existing RCT data to ascertain whether or not certain patient groups are more likely to benefit from this intervention.
- There was low-level evidence for pain relief in the short, intermediate and long term using sodium hyaluronate for LET. An intervention-specific systematic review is required to establish the effectiveness in this condition; however, given that we identified only one subsequent RCT of this intervention, further RCTs are needed, assuming that there is clinical rationale for the use of this intervention.

- There was moderate-level evidence showing no benefits for pain relief in the short term using therapeutic ultrasound-guided injections of sclerosing solution for LET. An intervention-specific systematic review is required to establish the effectiveness in this condition; however, given that we only identified one subsequent RCT of this intervention, further RCTs are needed assuming there is clinical rationale for the use of this intervention.
- There was low-level evidence showing no benefits of glycosaminoglycan polysulphate injections on pain relief in the short term. An intervention-specific systematic review is required to establish the effectiveness in this condition; however, given that we identified only one subsequent RCT of this intervention, further RCTs are needed, assuming that there is clinical rationale for the use of this intervention.
- There was low-level evidence for large benefits in pain relief in the short term using injections of botulinum toxin for LET in the short term; however, the evidence regarding the potential benefit should be considered in the context of data relating to reported adverse events. Further evidence is needed to make a firm recommendation regarding the effectiveness of this intervention. Three subsequent RCTs were identified which had been included in two intermediate-quality reviews; however, sample sizes were small and studies were placebo controlled. We therefore recommend an updated, high-quality systematic review. We also recommend (1) conducting larger-scale, good-quality RCTs with an active control arm and sufficient follow-up and, (2) a subgroup analysis of existing RCT data to ascertain whether or not certain patient groups are more likely to benefit from this intervention.
- There was low-level evidence showing a large reduction in pain using prolotherapy for LET in the intermediate term. An intervention-specific systematic review is required to establish the effectiveness in this condition; however, given that we identified only one subsequent RCT of this intervention, further RCTs are needed, assuming that there is clinical rationale for this the use of this intervention.

Summary of cost-effectiveness review

For the cost-effectiveness review, the inclusion and exclusion criteria were the same as for the clinical effectiveness review, except study design, for which full cost-effectiveness analyses, cost–utility analyses, cost–benefit analyses and cost–consequence analyses were included.

From 183 titles and abstracts screened from the cost-effectiveness searches, 16 full papers were ordered and, of these articles, 13 were excluded. Three articles were included in the systematic review, of which two were published, trial-based economic evaluations and one was an abstract of a model-based economic evaluation. The last is briefly discussed but not formally included.

- Both included studies were evaluated against the Evers checklist (Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care* 2005;**21**:240–5) and considered to be of good quality. One study did not conduct sensitivity analysis and the generalisability of results to other settings is unclear.
- No significant differences between interventions were reported in terms of effectiveness. Differences in costs were reported, but the study was underpowered to detect significance in this respect.
- The evaluations showed that GCIs may be more cost-effective in the short term by facilitating earlier return to work. Physiotherapy was found to be more cost-effective in the longer term. However, the estimates of effectiveness relied on the accompanying trials that were too small to overcome uncertainty about the size of the effects.

The existing evidence on economic outcomes is considered to be insufficient to inform decision-making in the context of the research question specified in this review.

Conclusions

Clinical effectiveness evidence from the high-quality systematic reviews identified in this overview continues to show uncertainty as to the effectiveness of many conservative interventions for the treatment of LET.

Although new RCT evidence has been identified comparing active comparators with placebo; these studies are, largely, made up of small sample sizes and as such give rise to uncertainty as to the size of reported effects within them.

Conclusions concerning cost-effectiveness are also unclear. Although the two economic evaluations identified were considered good quality, the accompanying trials on which they are based are too small to overcome uncertainty about the size of effects reported. One health economic model was identified, but this was available only in abstract format and, thus, was not included in our review.

We consider that the primary focus should be on conducting large-scale, good-quality clinical trials, with a core set of outcome measures (for defined time points) and appropriate follow-up. In addition, we also consider that subgroup analysis of existing data may be beneficial to ascertain whether or not certain patient groups are more likely to respond to treatments. In some cases, however, updated or new systematic reviews would also be of value.

Strengths and limitations

The overview of clinical effectiveness systematic reviews and systematic review of cost-effectiveness studies were conducted by an independent research team using the latest evidence and to a prespecified protocol (PROSPERO CRD42013003593).

Limitations were identified as follows:

- The approach used was to identify the number of systematic reviews and to quantify the number of RCTs not included in a recent systematic review. Thus, the RCTs were not quality appraised and we only presented a summary of study characteristics for information purposes.
- The searches were limited to English language because of resource limitations, which may have led us to exclude important studies.
- Epicondylitis is characterised by pain and tenderness in the lateral (tennis elbow) or medial (golfer's elbow) humeral epicondyle (Shiri R, Viikari-Juntura E. Lateral and medial epicondylitis: role of occupational factors. *Best Prac Res Clin Rheumatol* 2011;**25**:43–57). However, this review focuses on lateral epicondylitis as the condition is more common than medial epicondylitis.
- We did not consider uncontrolled studies or systematic reviews of uncontrolled studies to assure high quality with minimum risk of bias.
- We did not consider dosing studies; however, it is unclear whether or not these studies would add to the findings of the review.
- We did not consider global improvement (or other dichotomous outcomes), which has been shown to add value.
- The summary of findings was based only on high-quality evidence, i.e. only three of the five systematic reviews scoring 8 points or higher on the AMSTAR measurement tool and subsequently assessed using GRADE (because of a lack of reported data, two studies were not analysed using the GRADE principles).
- Few economic evaluations ($n = 2$) reported the cost-effectiveness of conservative interventions for the treatment of LET. The evaluations took effectiveness estimates from accompanying trials that had small sample sizes and, as such, there was uncertainty surrounding the effect sizes reported. This, in turn, leads to uncertainty of the reported cost-effectiveness and therefore no robust recommendations could be made in this respect.

Research recommendations

- Update systematic review: ESWT, low-level laser therapy (LLLT), therapeutic ultrasound, exercise, GCIs, botulinum toxin, acupuncture (Green SBR, Barnsley L, Hall S, White M, Smidt N, Assendelft W. Acupuncture for lateral elbow pain. *Cochrane Database Syst Rev* 2002;**1**:CD003527), combination physiotherapy, non-steroidal anti-inflammatory drugs (NSAIDs) [update to Cochrane review of NSAIDs published May 2013 (subsequent to completion of this review): Pattanittum P, Turner T, Green S, Buchbinder R. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating lateral elbow pain in adults. *Cochrane Database Syst Rev* 2013;**5**:CD003686].
- Conduct systematic review: no high-quality systematic reviews identified and few RCTs: wait-and-see/watch-and-wait, sodium hyaluronate, therapeutic ultrasound (sonographically)-guided injection of sclerosing solution, glycosaminoglycan polysulphate injections, orthotics, manipulation, Cyriax physiotherapy, soft-tissue therapy, iontophoresis, cryotherapy, myofascial release, electrical stimulation, platelet-rich plasma (PRP) injection and autologous blood injection (ABI) [Cochrane review of platelet-rich therapies published December 2013, subsequent to completion of this review: Moraes V, Lenza M, Tamaoki MJ, Faloppa F, Belloti JC. Platelet-rich therapies for musculoskeletal soft-tissue injuries. *Cochrane Database Syst Rev* 2013;**12**:CD010071, and ABI in progress: Silagy M, O'Bryan E, Johnston RV, Buchbinder R. Autologous blood and platelet rich plasma injection therapy for lateral elbow pain (Protocol). *Cochrane Database Syst Rev* 2014; **2**:CD010951].
- Focus on conducting larger-scale, good-quality RCTs: LLLT, ESWT, therapeutic ultrasound, combination physiotherapy, exercise, GCI (longer-term effects), botulinum toxin (longer-term effects) and wait-and-see/watch-and-wait. In addition, assuming there is a clinical rationale for this intervention in the indication under review, sodium hyaluronate, therapeutic ultrasound (sonographically)-guided injection of sclerosing solution and glycosaminoglycan polysulphate injections.
- Subgroup analysis of existing trial data: GCIs, botulinum toxin and exercise.

Study registration

This study is registered as PROSPERO CRD42013003593.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 12/73/01. The contractual start date was in January 2013. The draft report began editorial review in May 2013 and was accepted for publication in January 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).