

Pulsed low-intensity ultrasound therapy for chronic lateral epicondylitis: a randomized controlled trial

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Objectives. Pulsed low-intensity ultrasound therapy (LIUS) has been found to be beneficial in accelerating fracture healing and has produced positive results in animal tendon repair. In the light of this we undertook a randomized, double-blind, placebo controlled trial to assess the effectiveness of LIUS vs placebo therapy daily for 12 weeks in patients with chronic lateral epicondylitis (LE).

Methods. Patients with LE of at least 6 weeks’ duration were recruited from general practice, physiotherapy and rheumatology clinics, and had to have failed at least one first-line treatment including non steroidal anti-inflammatory drugs (NSAIDs) and corticosteroid injection. Participants were assigned either active LIUS or placebo. Treatment was self-administered daily for 20 min over a 12-week period. The primary end-point was a 50% improvement from baseline in elbow pain measured at 12 weeks using a patient-completed visual analogue scale.

Results. Fifty-five subjects aged 18–80 were recruited over a 9-month period. In the active group 64% (16/25) achieved at least 50% improvement from baseline in elbow pain at 12 weeks compared with 57% (13/23) in the placebo group (difference of 7%; 95% confidence interval –20 to 35%). However, this was not statistically significant ($\chi^2 = 0.28$, $P = 0.60$).

Conclusion. In this study LIUS was no more effective for a large treatment effect than placebo for recalcitrant LE. This is in keeping with other interventional studies for the condition.

KEY WORDS: lateral epicondylitis, tennis elbow, low intensity ultrasound (LIUS), treatment.

Lateral humeral epicondylitis (LE) is a tendinopathy of the common extensor–supinator tendon of the elbow characterized by lateral peri-epicondylar pain exacerbated by gripping. First described by Runge [1], LE is a soft-tissue lesion affecting men and women equally, with a reported incidence of up to 3% in the population and a peak occurrence in the fifth decade [2].

Despite the commonly used term ‘tennis elbow’, fewer than 5% of sufferers play regular predisposing sport [3], although up to 50% of regular tennis players in the USA are said to be affected at some time in their playing life [4]. Symptom development is felt to occur in the contralateral arm as a result of favouring this limb [5]. Development of LE is usually insidious, although the onset may result from strenuous overuse relating to particular repetitive actions. The duration of LE is highly variable, ranging from 3 weeks to several years [4]. With the avoidance of aggravating factors, most cases resolve spontaneously within 12 months [6]. Interventional studies of this disorder have been disappointing and evidence is lacking for the long-term benefit of physical therapies [7, 8].

Low-intensity ultrasound therapy (LIUS) has been shown to be beneficial in accelerating fracture healing and has produced positive results in animal tendon repair [9–12; J. Huckle, A. Jackson, A. Carter, W. Walsh. Internal report, Smith and Nephew, 2002; L. Zongyu, S. Sampson, C. Rubin, K. McLeod. Internal report, Smith and Nephew, 2000]. In the light of this we undertook a trial to assess the effectiveness of LIUS in patients with chronic LE.

Patients and methods

Study design

A double-blind randomized controlled trial was conducted in tertiary care to assess the benefit of LIUS in chronic LE. Consecutive patients aged between 18 and 80 yr were recruited who had consulted their general practitioner (GP), physiotherapist or rheumatologist with LE for more than 6 weeks. All had failed at least one first-line treatment, including topical or oral NSAIDs, corticosteroid injection and physiotherapy. The study was undertaken over a 12-month period, with recruitment lasting 9 months.

Patients were invited to attend an initial screening clinic and were assessed for their suitability, including demographic information and baseline measurements (Table 1). For reference purposes, the details of the inclusion and exclusion criteria are included in an additional table to be found as supplementary data at *Rheumatology* Online.

Treatment allocation was according to a study number following patient inclusion corresponding to that on the LIUS treatment pack. The assignment scheme was generated from a table of random numbers held by the sponsoring company (Smith and Nephew). In patients with bilateral involvement, each elbow was randomized separately.

Any analgesic apart from paracetamol was stopped on initial contact, with a 1-week washout period prior to the baseline assessment. Referring physicians were informed of the patient’s

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TABLE 1. Personal and clinical characteristics

	Active group (n = 29)	Placebo group (n = 30)
Age (yr): median (interquartile range)	51 (45–57)	50 (46–57)
Sex (M/F)	11/8	13/17
Number of individuals playing regular sport (>2 h week)	4	2
Hand dominance (right/left)	(29/0)	(29/1)
Percentage of subjects with non-dominant arm affected	34% (10)	20% (6)
Number of episodes at presentation		
First	11	11
Second	8	4
Recurrent	10	15
Time since onset of current episode: median (range)	8 (4–36)	9 (3–48)
Circumstances of onset: non-traumatic/traumatic	28/1	30/0
Previous management of condition		
NSAID	22	24
Topical NSAID	6	4
Corticosteroid injection	12	10
Physiotherapy	2	4
Acupuncture	1	1
Orthosis support	3	4
Health-care workers consulted		
GP	29	30
Physiotherapist	2	4
Consultant	3	7

participation and were requested not to commence any new therapy without contacting the study investigators.

Treatment protocol

Subjects self-administered the LIUS device throughout the trial following demonstration of its use at enrolment. This involved placement of the ultrasound probe over the point of maximal tenderness in the region of the lateral epicondyle. A simple 'on' switch began a timed 20-min countdown of therapy. A coupling gel was applied to the probe and patients were instructed to use the device daily over a 3-month period. Compliance was monitored by retrieval of information from the device detailing the number of 20-min completed sessions.

Subjects were randomized and all appliances were identical and appeared to be fully functional. Active devices produced a low-intensity (30 mW/cm²), 1.5 MHz ultrasound signal modulated by an ON/OFF square function. Placebo devices did not emit an ultrasound signal.

The primary outcome measure was a 50% improvement from baseline in elbow pain measured at 12 weeks using a patient-completed visual analogue scale (VAS). Patients were asked to place a mark along a 100-mm scale to indicate how much elbow pain they had suffered in the previous week (0 mm representing no pain, 100 mm representing worst pain imaginable). Secondary end-points included a 50% improvement from baseline in pain and function scores using the Patient-Related Forearm Evaluation Questionnaire (PRFEQ) [13], grip strength, and a summary status of local injury questionnaire [14, 15]. These measurements were collected at baseline and 6 and 12 weeks by the same blinded assessor.

An average of three measurements of maximum grip strength was taken using a digital grip myometer. Comparing the difference in grip strength between the non-involved and involved arms was done to eliminate the influence of intersubject variability.

The PRFEQ involved five items relating to pain and 10 items relating to difficulty carrying out particular tasks involving the forearm [13]. The items on the pain and function subscale of the

PRFEQ were scored using a 10-cm visual numeric rating scale with anchors of 0 (no pain at all) and 10 (worst pain imaginable). The mean result from the five pain and 10 functional questions gave the pain and function scores, respectively.

The summary item status of local injury was determined by proposing the question 'How is your elbow today?' with the option of a five-item response (very bad/bad/fair/good/very good) [14, 15].

The question about pain over a 'one week period' in the VAS and PRFEQ aimed to minimize the effect of any acute flare on the estimate of pain and function.

During the course of the study, patients were withdrawn if they fell into one of the following two categories: (i) co-interventions including corticosteroid injections, physiotherapy, NSAIDs, oral corticosteroids or surgery; (ii) patient request.

The ethics committee at Addenbrooke's NHS Trust approved the study and all subjects were fully counselled by a member of the research team (A.P.D.) and informed consent was obtained.

Statistical analysis

The study was planned to recruit 30 patients per group. This provided 80% power to detect a 0.35 difference between groups in the proportion of patients improving by 50% from baseline in elbow pain at 12 weeks, allowing for 10% attrition. This was based on a proportion of 0.5 of patients improving by 50% in the placebo group. All hypothesis tests were two-tailed and a *P*-value of 0.05 was considered statistically significant. Comparison of the difference from the baseline values for both treatment groups at 6 and 12 weeks was made. The analyses were carried out according to a protocol. Continuous data were compared between groups using the Mann-Whitney U-test and categorical data with Fisher's exact test. Analyses were carried out with SPSS version 12.0 (available at www.spss.com).

Results

Eighty-one subjects were contacted and invited to take part in the trial. A total of 69 subjects attended clinic, two failed to respond to initial contact efforts, one did not attend the appointment and in a further nine symptoms had resolved.

Fourteen subjects were excluded: nine did not meet inclusion criteria and five were misdiagnoses. Subjects were well matched for chronicity and previous therapy (Table 1).

Forty-eight cases successfully completed the trial (Fig. 1), two participants being excluded due to protocol violation.

Primary outcome measure: visual analogue scale of pain

At 12 weeks pain had improved in all but six subjects (four in the active group, two in the placebo group). In the active group the median percentage reduction in pain from baseline was 80% compared with 63% in the placebo group. Sixty-four per cent (16/25) in the active group had a greater than 50% improvement compared with 57% (13/23) in the placebo group; the difference was 7% (95% confidence interval -20% to 35%). However, this was not statistically significant ($\chi^2 = 0.28$, *P* = 0.60) (Table 2).

Secondary outcome measures

Using the PRFEQ, pain scores had improved in all but six subjects (three in the active group, three in the placebo group). Pain scores in one patient who received active treatment remained the same. The median improvement in pain from baseline was 48% in the active treatment group and 43% in the placebo group. There was no statistically significant difference in PRFEQ pain scores

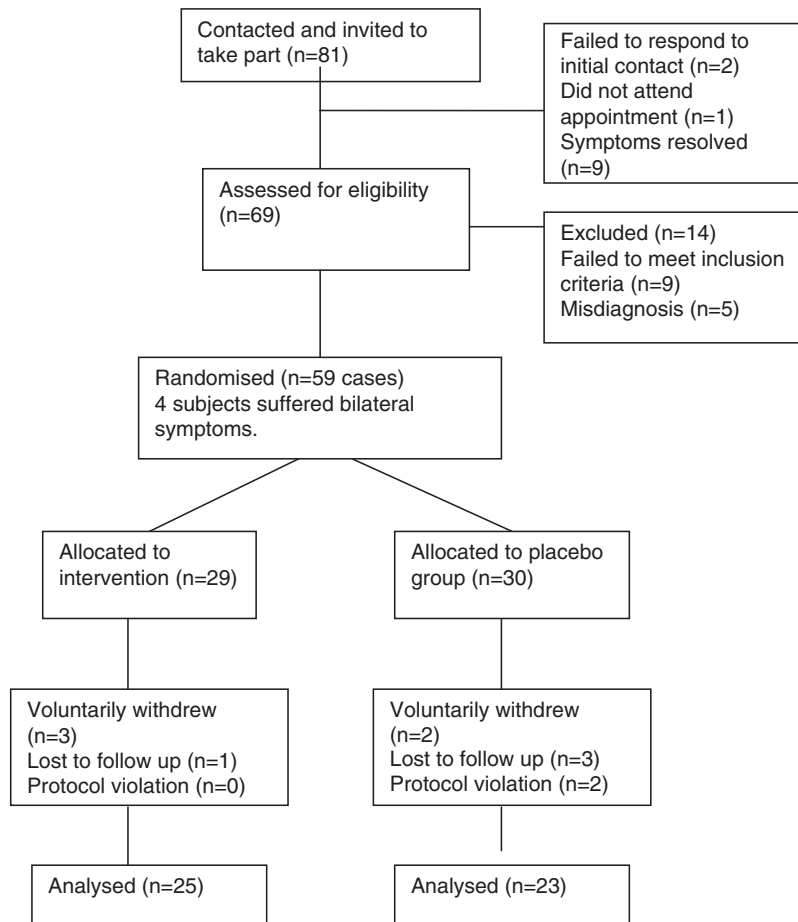


FIG. 1. Flow of participants through each stage of the randomized trial.

TABLE 2. Median and interquartile range (IQR) for the percentage change in both groups for the pain VAS and PREFEQ outcome measures

	Active	Placebo	Total
VAS score: median (IQR)	80% (42%, 97%)	63% (29%, 94%)	
<50% improvement	9 (36%)	10 (43%)	19
>50% improvement	16 (64%)	13 (57%)	29
Pain score	48% (22%, 82%)	43% (19%, 70%)	
<50% improvement	13 (52%)	12 (52%)	25
>50% improvement	12 (48%)	11 (48%)	23
Function score	66% (24%, 92%)	49% (24%, 87%)	
<50% improvement	10 (40%)	12 (52%)	22
>50% improvement	15 (60%)	11 (48%)	26

between the active and placebo groups ($\chi^2 = 0.0001$, $P = 0.99$) (Table 2).

A similar pattern was observed in PRFEQ function impairment scores. At 12 weeks there was no statistically significant difference in PRFEQ function scores between the active and placebo groups ($\chi^2 = 0.72$, $P = 0.40$) (Table 2). There was no evidence of differences in the median improvement level between the active and placebo groups (U-test not significant).

For the secondary outcome measure of grip strength, the median percentage reduction between the affected and unaffected arms at 12 weeks was 73% in the active group and 62% in the placebo group. After 12 weeks the difference in grip strength had widened in five subjects, one of whom one was receiving active therapy. There was no statistically significant difference between active and placebo groups ($P = 0.45$, U-test) (Table 3).

No statistically significant difference was found between the active and placebo groups with respect to the summary item of status of local injury using Fisher’s exact test at either 6 or 12 weeks.

Compliance with the device was high; it was used on 75 out of a possible 84 days. LIUS was well tolerated and there were no reported side-effects of treatment. A formal assessment of patient blinding was not performed.

Discussion

Multiple interventional trials for chronic LE have not shown any benefit for active treatment over placebo. These studies assessed a variety of modalities, including ultrasound, pharmacological and physical therapies [16–34].

It is not possible to directly compare the outcome of our trial with these previous studies; however, a common conclusion is the lack of distinguishable benefit from active intervention.

In our group of subjects with LE the majority of cases arose spontaneously. In those subjects who voluntarily withdrew, all did so as a result of the perception that the treatment was ineffective; three of the five acknowledged it was due to continuation of their manual job. It is possible that not all of our cases were LE but other pathology, such as enthesopathy; however, the rationale of treatment reduces this concern.

LIUS requires high patient motivation due to the length of therapy. Despite this drawback, use was high, as indicated by the monitoring results from the device.

The most common presenting symptom of LE is pain and this is the most frequently used outcome measure in clinical trials.

TABLE 3. Median and interquartile range (IQR) for the difference in percentage reduction in grip strength between affected and non-affected arms in each group

	Active group		Placebo group		Mann-Whitney U-test U (P)
	Median (IQR)	n	Median (IQR)	n	
Percentage reduction in difference of grip strength from baseline to 6 weeks	46% (7%, 69%)	20	37% (2%, 65%)	18	164 (0.64)
Percentage reduction in difference of grip strength from baseline to 12 weeks	73% (51%, 85%)	21	62% (27%, 88%)	22	200 (0.45)

Several validated scoring systems exist for assessing pain and we selected the VAS as the preferred assessment modality due to its repeatability and validity.

The development of the PRFEQ [13] provided an uncomplicated, standardized quantitative method for assessing both pain and functional disability associated with elbow disorders.

Grip strength improved over the duration of the trial and no difference was found between the two groups. One of the limitations of grip strength is its subjectivity, being reliant on patient effort, which may vary greatly between individuals.

The statement of local injury summary has not been used previously for patients with LE; however, it was considered an appropriate outcome measure as it has previously been found to be a valid and reliable indicator of quality of life [14, 15].

The selection criteria we used required patients to have failed at least one first-line therapy. This may have biased our study to include a more recalcitrant group. Four patients were included with bilateral symptoms and it is reasonable to assume that the response to therapy would be similar in both elbows, leading to a clustering effect. As the number was small we do not feel that inclusion of these cases had an appreciable effect on the study results.

Our study has excluded the possibility of a large treatment effect of LIUS therapy (i.e. a difference between LIUS therapy and placebo of 35% of patients improving by 50% from baseline). A study of around 200 patients would be required to detect a moderate treatment effect (i.e. 20% difference).


In our study the vast majority (81%, 39/48) of subjects, whose mean duration of symptoms was 9 months, improved at 12 weeks. Spontaneous resolution is said to occur most commonly by 12 months; thus, our patients may have improved regardless of intervention [6]. Therefore this trial may not have provided a true reflection of the usefulness of LIUS. Inclusion criteria of at least 12 months of unresolved LE symptoms following one or more cortisone injections may be more appropriate in future studies.

Conclusion

This randomized controlled trial discounted a large treatment effect for LIUS in the treatment of chronic LE. A more moderate effect may be achieved, but to detect this would require a larger study.

The authors declare no conflict of interest.

Supplementary data

 Supplementary data are available at *Rheumatology* Online.

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