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Effectiveness of ultrasound therapy for the treatment of lateral elbow tendinopathy (the UCICLET trial): study protocol for a three-arm, prospective, multicenter, randomised controlled trial

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Author Contributions

SZY and CS are the primary investigators.

SZY, CS, LWX, ZYY, FCY participated in the development of the study design.

SZY, CS, LWX, SGX, LJJ, WJ, WW, ZYY, and FCY participated in the study conduct.

SZY, CS and LWX drafted the manuscript under FCY's supervision.

FCY contributed to applying for and gaining funding.

All authors contributed to the content and critical revision and approved the final draft of the manuscript.

Conflict of interests

The authors, their immediate families, and any research foundation with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

The authors declare no competing financial interests.

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ETHICS

The Ethics Committee of the 4 clinical centers have approved this study. The Ethics Committee approval number of the leading clinical center (Shanghai Sixth People's Hospital) is 2021-153. The research registry number is ChiCTR2100050547 at http://www.chictr.org.cn. Data will be analyzed anonymously; all patients will approve the results of this study by oral consent. The oral consent approval will be documented in the patients' files. All clinical investigations will be conducted in accordance with the guidelines of the Declaration of Helsinki.

ABSTRACT

Introduction

Lateral elbow tendinopathy (LET) is a highly prevalent disease among middle-aged population, with no consensus on optimal management. Nonoperative treatment is generally accepted as the first-line intervention. Ultrasound (US) therapy has been widely reported to be treatment beneficial in various orthopedics diseases including tendinopathy. The purpose of this study is to investigate the effectiveness of US for LET treatment.

Methods and analysis

This protocol entails a three-arm, prospective, multicenter, randomised controlled trial. 72 eligible participants with clinically confirmed LET will be assigned to either (1) US, (2) Corticosteroid Injections or (3) control group. All participants will receive an Exercise-based Therapy as fundamental intervention. Primary outcome is Patient-Rated Tennis Elbow Evaluation. Secondary outcomes included Visual Analogue Scale for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand for upper limb disability, pain free/maximum grip strength, Work Limitations Questionnaire-25 for functional limitations at work, EuroQol-5D for general health, Hospital Anxiety and Depression Scale for mental status, Global Rating of Change for treatment success and recurrence rate, and Mahomed scale for participant's satisfaction. Adverse events will be recorded. Intention-to-treat analyses will be used.

Ethics and dissemination

Ethics Committees of all clinical centers have approved this study. The leading center is Shanghai Sixth People's Hospital, whose approval number is 2021-153. New versions with appropriate amendments will be submitted to the committee for further

approval. Study results will be published in peer-reviewed journals and presented at local, national and international conferences.

Trial registration number

ChiCTR2100050547.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Exercise-based Therapy as fundamental intervention for all participants with lateral elbow tendinopathy (LET).
- The first randomised controlled trial (RCT) to compared the efficacy between ultrasound therapy and corticosteroid injections in LET treatment.
- Multicenter RCT with blinded outcome assessor and statistician.
- Use of several patient-reported outcome measures as well as objective parameters.
- Participants and treating surgeons not blinded.

INTRODUCTION

First described by Runge,[1] lateral elbow tendinopathy (LET), also widely known as tennis elbow, has an estimated prevalence of 1% to 3% in the general population, and peaks at fourth and fifth decades of life, with an equal gender distribution.[2] LET causes great burden on social economy, with an annual sickness absence rate as high as 5% in the working-aged adults.[3] Though previously considered to be a "tendinitis", histological analysis suggests a degenerative rather than an inflammatory process in LET, which is now commonly converted to be considered as a "tendinosis".[4] A LET diagnosis is usually straightforward, with clear clinical signs and symptoms. Patient most often complains of pain at or around the bony surface of the upper half of the lateral epicondyle, and is likely to have a history of strenuous overuse relating to particular repetitive actions in the affected upper limb.[5,6]

Though LET usually is a self-limiting condition, but complaints may last up to 2 years or longer,[7] therefore, it has great clinical value to find a better and faster recovery process. General principles of LET treatment should be orientated to pain relief, movement restoration, grip strength and endurance improvement, back to normal function and life quality, and control of further clinical deterioration.[8] Surgery is only considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population;[2] therefore, nonoperative treatment is suggested as first-line treatment.[9]

To date, though the treatment method is vast; however, no successful and universally accepted regimen has been established. In a cross-sectional survey of UK practice in managing LET, 81% experts recommended Exercise-based Therapy (EBT) as the first-line intervention.[10] EBT was also supported by high quality clinical trials[11-13] and systematic reviews[14,15], regarding as the most cost-effective treatment for LET.[16]

The survey also showed, though the recurrence rate may be high and prognosis may be worsened in the long term,[11-13] the long mainstay treatment traditionally - corticosteroid injection (CI), due to its use for quick pain relief and physical functioning improvement, was still the most recommended first-line intervention apart from EBT and second-line intervention (27%).[10] In additional, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hyaluronate injection,[17] platelet-rich plasma injection,[18] extracorporeal shock-wave therapy[19] and acupuncture[20] still remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. US can reduce muscle spasms and pain, and facilitate tissue repair by increasing local blood flow and stimulating inflammatory mediators.[21] US has been widely reported to be treatment beneficial in fracture nonunions,[22,23] osteoarthritis,[24,25] chronic muscle pain,[26,27] soft tissue injury,[28] etc. As for tendinopathy, US is also reported to be a potential noninvasive treatment modality for frozen shoulder,[29,30] rotator cuff,[31] achilles[32,33] and patellar[34] tendinopathy. Some studies have reported the efficacy of US in LET treatment, but with low grade of study design and data,[35] and most of them focused on the comparison between US and extracorporeal shockwave therapy[36-40]. Therefore, the role of US in LET treatment still needs to be further explored by high-quality study. Additionally, to our best of knowledge, no study has compared the efficacy between US and CI in LET treatment yet.

Therefore, the purpose of the current three-arm, prospective, randomized, multicenter trial is to investigate the effectiveness of US in treatment for LET, that is, US versus CI versus control, with a fundamental intervention of EBT, on clinical and functional outcomes, including Patient-Rated Tennis Elbow Evaluation (PRTEE) in patients diagnosed with LET.

METHODS

Study design

The design of this study is a three-arm, prospective, multicenter, randomised controlled trial, that will enroll participants with a diagnosis of chronic symptomatic LET from 4 municipal tertiary hospitals (Shanghai Sixth People's Hospital, Shanghai Tenth People's Hospital, Shanghai East Hospital, and Pudong New Area People's Hospital of Shanghai). This manuscript is written according to the SPIRIT guidelines.[41]

Participant and public involvement

This study was done without participant involvement. Participants were not invited to comment on the design and not consulted to develop patient-relevant outcomes. Participants will not be invited to contribute to the writing or editing of this manuscript for readability or accuracy. The resulting publications will be disseminated to public via mass media. Participants as a whole will be acknowledged in the end of our publications and presentations.

Participant recruitment

Figure 1 shows the participant flow chart throughout the study. Participants will be recruited over a period of 5 months, from the intake clinics of 4 principals of each sub-centers. Additionally, we will recruit participants through other physicians and healthcare professionals, via the hospital intranet, community and medical association newsletters, etc. Those interested will contact the research assist who will provide further information about the study objectives and procedures and will perform an initial eligibility screening interview by telephone.

Medical evaluation and enrolment procedure

Participants found to be eligible will be invited to attend a medical examination, to confirm the LET diagnosis and assess eligibility to participate in the research project.

Inclusion criteria

- Age ≥18 years old;
- Unilateral lateral elbow pain longer than 6 weeks duration;
- Pain over the lateral humeral epicondyle with pain severity of greater than 30 mm on a 100-mm visual analog scale (VAS), provoked by at least 2 of the following: gripping, palpation, resisted wrist or middle finger extension, or stretching of forearm extensor muscles with reduced pain-free grip;[11,42]
- Able to read and write in simplified Chinese (Mainland), understand and complete the questionnaire, and should provide informed consent.

Exclusion criteria

- Concomitant musculoskeletal pain conditions reported by participants to be their predominant complaint within the past 6 months;
- History of symptoms suggesting radicular, neurological, inflammatory or systemic arthritic conditions;
- Treatment by physiotherapy, electrophysical therapy, or injection within the past 6 months, or previous tennis elbow surgery;
- Contraindications to US, including dermatological conditions, abnormal sensation in the affected arm, indwelling electrical pumps/pacemakers, epilepsy, pregnancy or breastfeeding, et al.;
- Contraindications to CI, including hypertension, gastrointestinal ulcers, diabetes, mental illness, et al.

Following the medical evaluation, a research assistant will meet with the eligible participants and obtain written informed consent. Demographic variables will be reported before treatment (baseline) of all participants regarding age, sex, body mass index, affected elbow, dominant arm, lifestyle (smoking and drinking), and previous

medical history. Participants will also be asked relevant questions about duration of symptoms and previous treatments (rehabilitation exercises, injections or others). Others like occupation, employment characteristics (full-time or part-time work, manual or non-manual labor), employment status (whether on sickness absence), and professional activity characteristics (repetitive movements for >4hours/day; wrist flexion for >2hours/day; elbow flexion and extension for >2hours/day; use of computer keyboard/ mouse [how many hours/day] and use of vibrating instruments for >2hours/day) will be also collected.

Randomization and blinding

Participants will be randomized in three intervention groups (either US or CI or control arm) in a ratio of 1:1:1, using a computer-generated randomized sequence with varying unknown block sizes (either 3 or 6) for all study centers, without stratification. A research assistant with no involvement in the clinical care and evaluations of participants will prepare sequentially numbered, opaque, sealed envelopes according to the randomization lists, with security in place to ensure allocation data cannot be accessed or influenced by any person. At the appropriate time, this assistant will open the envelope and assure coordination of the therapeutic interventions.

The outcome assessor and statistician will be blinded to group allocation and not involved in treatment procedures.

Intervention

At the beginning, all participants will receive standardized education and advice on adjusting activity patterns and managing pain, which will be distributed in the form of printed brochures and orally assessed on their understanding of the content. Participants will be told that absolute rest of the arm will not be advocated, and activities that do not cause elbow pain should be encouraged. The primary physical impairment

in LET, which occurs in the muscle system, is best characterized as a deconditioning response of the forearm muscles to the pain. Therefore, all participants will receive the internationally best recommended fundamental intervention, EBT program, for the forearm muscles.[10] The EBT in this study will follow a standard protocol that has been adopted and used by several high-quality RCTs,[11,13,43,44] mainly for addressing motor impairments, relieving pain and stimulating tendon remodeling. 30 minutes per day, including basic tasks (pain free [1] gripping and [2] extension exercise) and appendage tasks ([3] flexion, [4] supination and pronation, and [5] radial and ulnar deviation exercise). Various kinds of resistance and load can be used, like free weights, rubber bands, manual resistance, isokinetic dynamometry or isometric contractions. [6] It is essential that all exercises that are performed for the upper limb must be done with sound alignment of the spine, trunk and proximal arm.

1) Pain-free gripping exercise with exercise putty, which allows practice of various different gripping actions.
2) Forearm extensor muscle exercise using a free-standing dumbbell. Note that the forearm is fully stabilized by the bench and upper body in sound postural alignment. Duration per repetition lasts about 6-10 s.
3) Dumbbell weight exercise for the forearm flexor muscle with 6-10 s per repetition. The postural is the same as 2).
4) Exercises for forearm supinator and pronator muscles using an imbalanced adjustable dumbbell weight with 6-10 s per repetition, from end range of supination to pronation with the participant maintaining full active control of the weight. The elbow bent to 90° with the arm stabilizing besides the trunk. Progressions in load imposed on the muscles can be achieved by increasing the weight or by increasing the distance between weight and hand.

5) Radial and ulnar deviation exercises are performed with similar equipment and guidelines in 4).

6) Education on recognition and correction of the poor posture from the pelvis to neck. Once the spine and trunk are aligned more optimally then the upper limb position should be addressed.

Participants in the [US group] will receive continuous mode US (Shanghai, China) at a frequency of 1 MHz and intensity of 1.0 W/cm^2 for 10 minutes in 5 days per week for 3 weeks on the maximum pain region of lateral elbow.

Participants allocated to the [CI group] will receive a single local infiltration of 1mL triamcinolone acetonide (10mg/ mL) and 1mL lidocaine 1%. Local corticosteroid injection was administered to the most painful area on pressure around the lateral epicondyle. Participants will be advised to wait for 20 min following injection, and to inform their doctor if there is any suggestion of infection or other adverse events. All adverse reactions will be managed by a committee chaired by the chief investigator. Rest from all strenuous activity for 1-2 weeks following injection will be strongly recommended, followed by gradual return to normal activities. Participants will be instructed to avoid aggressive return to activities even if substantial relief is obtained, to minimize potential recurrence of their symptoms.

Participants randomized to the [Control group] will neither receive US therapy nor corticosteroid injection. They will only receive the fundamental intervention, EBT program.

We discouraged additional treatments to that assigned (that is, not per protocol) during the intervention period, but we allowed the use of simple analgesics as needed. Participants reported all not per protocol treatments, such as drugs, in a diary.

Data management

Data will be collected during the participants' visits to the hospital at baseline, 3 weeks, 6 weeks and 3 months after random assignment (**Table 1**). In order to maximize participant compliance in follow-up completion, reminder emails and a telephone call by the research assistant will be programmed. Registered participants will be withdrawn from the study if: (1) participant withdraws his/her consent, and (2) exclusion criteria is discovered after registration. The reason and date of discontinuation will be recorded. Consent to use the data already collected prior to a participant's withdrawal will be included in the consent form.

Primary outcome measure

The primary outcome measure will be the difference in Patient-rated Tennis Elbow Evaluation (PRTEE). The PRTEE, formerly known as the Patient-Rated Forearm Evaluation Questionnaire, is a well validated composite scale measuring pain (5 items, with 0=no pain and 10=worst imaginable) and physical function (6 items for specific activities and 4 items for usual activities, with 0=no difficulty and 10=unable to do),[45] ranging from 0 to 100, with higher scores represent worse possible pain and more loss of function. The pain (intraclass correlation coefficients, ICC=0.89), physical function (ICC=0.83) and the total (ICC=0.89) scores all demonstrate excellent reliability.[46] A variation of 11/100 points or 37% of baseline scores are reported for clinical significance defined as "much better" or "completely recovered".[47] We use a validated Hong Kong Chinese version[48] of the PRTEE translated into simplified Chinese (Mainland) because the culture and language are the same.

Secondary outcome

Secondary outcome measures will be the differences in Visual Analogue Scale (VAS)[49] for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand (Quick-DASH)[50] for upper limb disability, pain free/maximum grip strength, Work

Limitations Questionnaire-25 (WLQ-25)[51] for functional limitations at work, EuroQol-5D (EQ-5D)[52] for life quality and health status, The Hospital Anxiety and Depression Scale (HADS)[53] for anxiety and depression status, Global Rating of Change (GROC) for treatment success and recurrence rate, and Mahomed scale[54] for participants' satisfaction.

■ Pain

The VAS will be used for pain evaluation, which consists of a 100-mm horizontal numbered line anchored at one end (0) with the words "no pain" and at the other end (100) with the words "worst pain imaginable", and whose score is determined by the distance between the left end of the line and the participant's mark in mm.[49] VAS is considered to be the most sensitive of all pain scoring scales and has been specifically validated in the LET population with high reliability (r=0.89) and a moderate correlation with pain-free grip strength (r=0.47).[55] Participants are asked to score their pain on this line during rest (at time of measure), provocation and maximum grip strength. The provocation test is conducted on the outpatient clinic by resisted dorsiflexion of the wrist during full elbow extension. Clinically relevant improvement will be defined when a 50% decrease in VAS is observed before and after the treatment.[56] The consumption of rescue medication taken by each patient will be also recorded at each follow-up visit.

■ Upper limb disability

The well-validated simplified Chinese (Mainland) version of Quick-DASH[57] will be used for elbow function evaluation, which consists of eleven questions scored on a 5-point scale similar to the DASH.[50] Total and individual module scores will be calculated out of 100, with a higher score indicating a worse status. A minimal clinically important difference of 15.91 points has been reported.[58]

■ Grip strength

Pain free/maximum grip strength will be measured using a dynamometer (CAMRY, City of Industry, CA, USA). The participants will be asked to take a shoulder-width stance and allow their arms to hang loose, holding their arm adducted along the body and the elbow in full extension. The pain-free grip strength will be measured, followed by the measurement of the maximum grip strength, and the affected side will be measured first and then the unaffected side. The measurement readings will be not revealed to the subjects until the completion of the test. The pain-free grip strength will be measured up to the point when the subject slowly squeezes the dynamometer until the occurrence of pain. The maximum grip strength will be measured at the maximum grip level. The mean of three consecutive trials, separated by a 20s pause, will be calculated. Results will be presented as a ratio of values of the symptomatic side/ asymptomatic side×100.[59]

■ Functional limitations at work

In order to gather information that is complementary to the pain and disability scales, functional limitations at work will be measured with the WLQ-25. It contains 25 items arranged under four subscales addressing four dimensions of job demands, those are, time demands, physical demands, mental/interpersonal demands, and output demands.[51] A five-level ordinal response scale ranging from 0 (all of the time) to 4 (none of the time) with an additional sixth option (does not apply to my job) is used. The total scores range from 0-100 points, and a 13-point (out of 100) improvement for the summed score is established for clinically important differences.[60]

■ Life quality and health status

The EQ-5D is one of the widely validated generic health-related quality of life (HRQol) measures known as its simplicity.[52] It contains a five-dimension descriptive

system (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a VAS, ranging from 0 to 1, in which 1 represents perfect health. All the dimensions are grouped into three levels (no problem, some problem and extreme problem). We used a validated Chinese version[61] of the EQ-5D, which has been recommended by China Guidelines for Pharmacoeconomic Evaluations 2011 for a measure for HRQol and health utility.[62]

■ Anxiety and depression status

HADS will be used to identify and quantify two of the most common psychological disorders - anxiety and depression.[53] There is evidence of increased levels of anxiety and depression in people with LET.[63] HADS is a 14-item scale independent of somatic symptoms, which consists of two 7-item subscales measuring depression and anxiety respectively. A 4-point scale (from 0 representing absence of symptoms, to 3 representing maximum symptomatology) is used. The total scores for each subscale range from 0 to 21, with higher scores indicating higher levels of disorder. HADS has two cut offs for categorization: 0-7, "non-case"; 8-10, "possible or doubtful case"; 11-21, "probable or definite case".[64]

■ Treatment success and recurrence rate

Participants' treatment impression of change regarding their condition will be recorded on a 6-point Likert scale (from "completely recovered", "much improved", "somewhat improved", "same", "worse" to "much worse"). Success rates will be calculated by dichotomizing responses. Participants who report their overall condition as "completely recovered" or "much improved" since the beginning of the study will be counted as successes, while other responses will be counted as failures.[11,13] Recurrence will primarily be defined as occurring when a participant rates a success at 3 weeks and a failure at 6 weeks or 3 months on GROC.[11,13]

■ Participants' satisfaction

Similarly, participants' level of satisfaction on the evolution of their condition will be determined on a validated 4-point Likert scale ranging from "very satisfied", "somewhat satisfied", "somewhat dissatisfied" to "very dissatisfied".[65]

Adverse events

All adverse events, defined as any negative or unwanted reactions to intervention, will be recorded through the symptoms reported by the patients, and observations by a researcher at every visit. US treatment may cause mild local swelling, spot-like bleeding, ecchymosis, enhanced local pain response, and local hyperesthesia or decrease. CI-related adverse events are divided into acute and long-term ones. Acute events include dizziness, skin flushing, local bleeding, and someone may even develop rarer physical reactions, such as arrhythmias. Therefore, all participants must take at least 20 minutes in the outpatient room to observe and even manage any acute adverse reactions following the injection. Long-term events may cause skin pigmentation, local calcification and infection.

Sample size calculation

Sample size and power calculation are based on the primary outcome of PRTEE score. All sample size calculations assume two-sided analysis with a power of 90% (1-β=0.90) at a significant level of α=0.05. Based on previous trial, a standard deviation (SD) of 5.1-point on PRTEE score will be used.[66] To detect a minimum clinically significant difference of 11.0-point[47] (superiority margin) between US and control groups (assuming a true difference of 15.6-point[38,66]), a total of 22 participants in each group is required. Allowing for an up to 10% drop out rate, we aim to enroll at least 24 participants in each group to complete the study.

Analysis plan

Baseline characteristics will be summarized for the three treatment groups using appropriate descriptive statistics. Both primary and secondary analysis will be conducted blind to treatment allocation and analyzed on intention-to-treat (ITT)[67] approach with all randomized participants retaining their original randomized group. Multiple imputation by chained equations will be used to address missing data caused by loss to follow-up and non-responses if these missing data are judged to be random.

The primary comparisons for PRTEE scores will be made using linear regression. In secondary analyses, repeated measures mixed model[68] will also be used to examine the associations between treatments and repeated outcome measures, with terms of treatment, time, trial center and corresponding baseline values as covariates (age, gender, body mass index, et al.). Linear regression will be used for numerical outcomes, and logistic/ordinal regression for any categorical outcomes.

Quality assurance/monitoring/management

A Manual of Operations and Procedures (MOP) and case report form will be developed as per protocol to standardize all procedures and staff training in areas such as patient recruitment, outcome measurement, data entry, management, analysis, and security, which also include the monitoring plans to assure patient protection and data integrity, thus facilitating consistency in protocol implementation and data collection. The investigators, physicians, research assistants, outcome assessors and statisticians are different people, and should receive Good Clinical Practice training. A trained project manager will visit each center for monitoring to ensure data quality and compliance with trial protocol.

All data obtained will be kept strict and stored electronically on a database with secured and restricted access. An encryption will be used for data transfer, with removal

for any information able to identify individuals. Data will be only deidentified for analysis at the completion of this study.

Study duration

Recruitment of the trial will begin in the November of 2021 and 3-month follow-up for all participants is anticipated to be completed by June 2022. See **Table 1** for time points and recruitment progress.

Ethics and dissemination

The study has been approved by all 4 Medical Ethics Committees (the approval number of the leading clinical center [Shanghai Sixth People's Hospital] is 2021-153) and will be conducted according to the principle of the Declaration of Helsinki (64th, 2013). All requirements regarding the welfare, rights and privacy of participants are fulfilled. The potential risks of this clinical trial are considered to be minimal and are addressed in the protocol and consent forms. A written consent will be obtained by clinical practitioners from each participant. The trial was registered on www.chictr.org website (registration number ChiCTR2100050547). Data will be published in peer-reviewed journals and presented at conferences, both nationally and internationally.

DISCUSSION

LET is a highly prevalent degenerative condition, which results in significant pain and limited function in the affected upper limb and causes great socioeconomic burden. Up till now, there is still no consensus on the optimal management, and nonoperative treatment is generally accepted as the first-line intervention. Multiple methods have been studied and reviewed in the recent decades, however, the exact efficacy still remains controversial and the evidence is very low.

Both Yalvaç B[38] and Özmen T[36] have shown significant improvements in terms of pain, upper limb function, strength and life quality from baseline after treatment with US. However, they did not have a blank control group, which would make it confuse and unclear whether the efficacy come from US itself or passing time, as LET is a self-limited disease. In this study, under the fundamental intervention of EBT program, the effects of US [US group] will be compared with blank [control group]. In additional, to the best of our knowledge, this study is the first to compared the efficacy between US [US group] and CI [CI group] in LET treatment. In clinic, US is less invasive, less expensive, safer and more portable than other nonoperative therapy like drug injections for tendinopathy and, if proved to be effective, could be offered to selected patients as part of non-operative therapy.

In view of recent literature, CI should be discouraged in the treatment of LET.[17,69] However, in order to satisfy the patient's need to relieve pain, CI are still commonly used in clinic. Therefore, a change in the paradigm of LET treatment is necessary. This change will come about through proposed evidence-based treatment guidelines. There are some on-going clinical trials on LET treatment recent years,[42,70,71] and our prospective RCT proposes to complement and add to this relevant and much needed scientific effort.

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multi-center, blinded, randomized controlled trial with a 1 year follow up. BMC Musculoskelet Disord. 2019;20(1):351.

Figure Legends

Figure 1 Participant flow chart

Table 1 Study evaluation procedures and timeline

Study procedure	Medical evaluation	Enrolment visit	3 weeks	6 weeks	3 months
Determine eligibility	√	√			
Obtain signed consent		√			
Obtain medical and demographic data		√			
Give instructions for Pain medication diary		√			
Outcome measures					
Patient-Rated Tennis Elbow Evaluation		√	√	√	√
Visual Analogue Scale for pain		√	√	√	√
Shortened version of the Disabilities of the Arm, Shoulder and Hand questionnaire		√	√	√	√
Pain free/maximum grip strength		√	√	√	√
Work Limitations Questionnaire-25		√	√	√	√
EuroQol-5D		√	√	√	√
Hospital Anxiety and Depression Scale		√	√	√	√
Treatment success rate			√	√	√

Treatment recurrence rate		√	√
Participants' satisfaction	√	√	√

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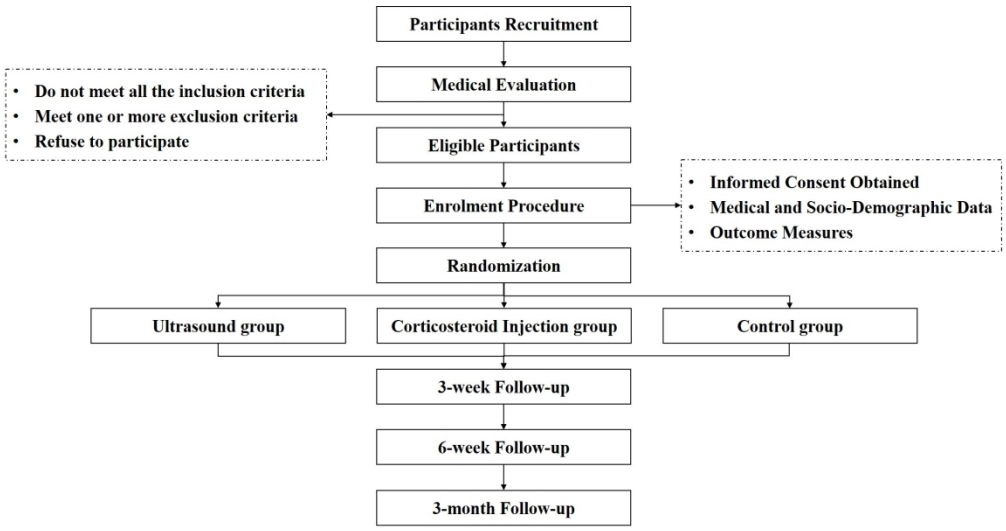

Participant flow chart

365x190mm (150 x 150 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	4/6

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4/6
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	2
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	2

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	8
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	10
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	11

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12-14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12-14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-14
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15-19
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	21

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15, 20-21
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15, 20-21
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	15, 20-21

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19-20
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	19-20
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15, 20-21
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15, 20-21
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	19

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	21
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	21
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	21
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	21
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	21
Declaration of	#28	Financial and other competing interests for principal	21

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15, 20-21
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	20-21
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20-21
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	20-21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20-21
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	/
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	/

BMJ Open

Effectiveness of ultrasound therapy for the treatment of lateral elbow tendinopathy (the UCICLET trial): study protocol for a three-arm, prospective, multicenter, randomised controlled trial

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Keywords:	Elbow & shoulder < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Orthopaedic sports trauma < ORTHOPAEDIC & TRAUMA SURGERY, REHABILITATION MEDICINE, SPORTS MEDICINE

TITLE PAGE

Title

Effectiveness of ultrasound therapy for the treatment of lateral elbow tendinopathy (the UCICLET trial): study protocol for a three-arm, prospective, multicenter, randomised controlled trial

Running Title

study protocol of UCICLET trial for lateral elbow tendinopathy

Keywords

Lateral elbow tendinopathy, randomised controlled trial, ultrasound therapy, corticosteroid injections, exercise-based therapy, Patient-Rated Tennis Elbow Evaluation

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Author Contributions

SZY and CS are the primary investigators.

SZY, CS, LWX, ZYY, FCY participated in the development of the study design.

SZY, CS, LWX, SGX, LJJ, WJ, WW, ZYY, and FCY participated in the study conduct.

SZY, CS and LWX drafted the manuscript under FCY's supervision.

FCY contributed to applying for and gaining funding.

All authors contributed to the content and critical revision and approved the final draft of the manuscript.

Conflict of interests

The authors, their immediate families, and any research foundation with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

The authors declare no competing financial interests.

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ETHICS

The study has been approved by all 4 Medical Ethics Committees, those are, Ethics Committee of Shanghai Sixth People's Hospital (the leading clinical center, approval No. 2021-153), Ethics Committee of Shanghai East Hospital (LL-2021-KYHZ-003), Ethics Committee of Shanghai Tenth People's Hospital (SHSY-IEC-4.1/21-193/01), and Ethics Committee of Pudong New Area People's Hospital (IRBY2021-005). The research registry number is ChiCTR2100050547 at http://www.chictr.org.cn. Data will be analyzed anonymously; all patients will approve the results of this study by written consent. The written consent approval will be documented in the patients' files. All clinical investigations will be conducted in accordance with the guidelines of the Declaration of Helsinki.

ABSTRACT

Introduction

Lateral elbow tendinopathy (LET) is a highly prevalent disease among middle-aged population, with no consensus on optimal management. Nonoperative treatment is generally accepted as the first-line intervention. Ultrasound (US) therapy has been widely reported to be a treatment that was beneficial for various orthopedics diseases including tendinopathy. The purpose of this study is to investigate the effectiveness of US for LET treatment.

Methods and analysis

This protocol entails a three-arm, prospective, multicenter, randomised controlled trial. 72 eligible participants with clinically confirmed LET will be assigned to either (1) US, (2) Corticosteroid Injections or (3) control group. All participants will receive an Exercise-based Therapy as fundamental intervention. Primary outcome is Patient-Rated Tennis Elbow Evaluation. Secondary outcomes include Visual Analogue Scale for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand for upper limb disability, pain free/maximum grip strength, Work Limitations Questionnaire-25 for functional limitations at work, EuroQol-5D for general health, Hospital Anxiety and Depression Scale for mental status, Global Rating of Change for treatment success and recurrence rate, and Mahomed scale for participant's satisfaction. Adverse events will be recorded. Intention-to-treat analyses will be used.

Ethics and dissemination

Ethics Committees of all clinical centers have approved this study. The leading center is Shanghai Sixth People's Hospital, whose approval number is 2021-153. New versions with appropriate amendments will be submitted to the committee for further

approval. Study results will be published in peer-reviewed journals and presented at local, national and international conferences.

Trial registration number

ChiCTR2100050547.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Exercise-based Therapy as fundamental intervention for all participants.
- The first randomised controlled trial (RCT) to compare the efficacy between ultrasound therapy and corticosteroid injections in lateral elbow tendinopathy treatment.
- Multicenter RCT with blinded outcome assessor and statistician.
- Use of several patient-reported outcome measures as well as objective parameters.
- Participants and treating surgeons not blinded.

1. INTRODUCTION

First described by Runge,[1] lateral elbow tendinopathy (LET), also widely known as tennis elbow, has an estimated prevalence of 1% to 3% in the general population, and peaks at fourth and fifth decades of life, with an equal gender distribution.[2] LET causes great burden on social economy, with an annual sickness absence rate as high as 5% in the working-aged adults.[3] Though previously considered to be a "tendinitis", histological analysis suggests a degenerative rather than an inflammatory process in LET, which is now commonly converted to be considered as a "tendinosis".[4] A LET diagnosis is usually straightforward, with clear clinical signs and symptoms. Patient most often complains of pain at or around the bony surface of the upper half of the lateral epicondyle, and is likely to have a history of strenuous overuse relating to particular repetitive actions in the affected upper limb.[5,6]

Though LET usually is a self-limiting condition, complaints may last up to 2 years or longer,[7] therefore, it has great clinical value to find a better and faster recovery process. General principles of LET treatment should be orientated to pain relief, movement restoration, grip strength and endurance improvement, back to normal function and life quality, and control of further clinical deterioration.[8] Treatments can be divided into operative and non-operative therapies. Invasive treatments commonly include open, arthroscopic and percutaneous release of the common extensor origin.[9] Among these, Ultrasonic Percutaneous Tenotomy, a recent developed method, appealing to many researches for its good durability of pain relief and functional recovery,[10] has a satisfied long-term (90 months) outcomes reported by Ang BFH.[11] However, surgery is usually considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population;[2] therefore, nonoperative treatment is suggested as first-

line treatment.[12] Generally, nonsurgical methods include injections (like corticosteroid, platelet-rich plasma, autologous blood, sodium hyaluronate, etc.), physiotherapy, extracorporeal shock-wave therapy (ESWT), ultrasound, topical glyceryl trinitrate, or oral naproxen, etc.[13,14]

So far, despite the wide range of treatments; however, there is no successful and universally accepted regimen. In a cross-sectional survey of UK practice in managing LET, 81% experts recommended Exercise-based Therapy (EBT) as the first choice of intervention.[15] EBT was also supported by high quality clinical trials[16-18] and systematic reviews[19,20], regarding as the most cost-effective treatment for LET.[21] The survey also showed that, as the mainstream treatment for a long time, corticosteroid injection (CI) was still the most recommended intervention second to EBT,[15] due to its quick pain relief and physical functional improvement, though the recurrence rate may be high and prognosis may be worsened in the long term.[16-18] In additional, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hyaluronate injection,[22] platelet-rich plasma injection,[23] ESWT[24] and acupuncture[25] still remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. US can reduce muscle spasms and pain, and facilitate tissue repair by increasing local blood flow and stimulating inflammatory mediators.[26] US has been widely reported to be treatment beneficial in fracture nonunions,[27,28] osteoarthritis,[29,30] chronic muscle pain,[31,32] soft tissue injury,[33] etc. As for tendinopathy, US is also reported to be a potential noninvasive treatment modality for frozen shoulder,[34,35] rotator cuff,[36] achilles[37,38] and patellar[39] tendinopathy. Some studies have reported the efficacy of US in LET treatment, but with low grade of study design and data,[40] and most of them focused on the comparison between US and ESWT[41-45]. Both Yalvaç B[43]

and Özmen T[41] have shown significant improvements in terms of pain, upper limb function, strength and life quality from baseline after treatment with US. However, they did not have a control group, which would make it unclear whether the efficacy come from US itself or passing time, as LET is a self-limited disease. Therefore, the role of US in LET treatment still needs to be further explored by high-quality study. Additionally, to our best of knowledge, no study has compared the efficacy between US and CI in LET treatment yet.

Therefore, the purpose of the current three-arm, prospective, randomized, multicenter trial is to investigate the effectiveness of US in treatment for LET, that is, US versus CI versus control, with a fundamental intervention of EBT, on clinical and functional outcomes, including Patient-Rated Tennis Elbow Evaluation (PRTEE). In view of recent literatures, CI should be discouraged in LET;[22,46] however, it's still common in clinic due to the ability of satisfying patient's need of quick pain relief.[15] Thus, a change in the paradigm of LET treatment is necessary. This change will come about through proposed evidence-based treatment guidelines. There are some on-going clinical trials on LET treatment in recent years,[47-49] and our prospective RCT proposes to complement and add to this relevant and much needed scientific effort.

2. METHODS

2.1. Study design

The design of this study is a three-arm, prospective, multicenter, randomised controlled trial, that will enroll participants with a diagnosis of chronic symptomatic LET from 4 municipal tertiary hospitals (Shanghai Sixth People's Hospital, Shanghai East Hospital, Shanghai Tenth People's Hospital, and Pudong New Area People′s Hospital of Shanghai). This manuscript is written according to the SPIRIT guidelines.[50]

2.2. Participant and public involvement

This study was done without participant involvement. Participants were not invited to comment on the design and not consulted to develop patient-relevant outcomes. Participants will not be invited to contribute to the writing or editing of this manuscript for readability or accuracy. The resulting publications will be disseminated to public via mass media. Participants as a whole will be acknowledged in the end of our publications and presentations.

2.3. Participant recruitment

Figure 1 shows the participant flow chart throughout the study. Participants will be recruited over a period of 5 months, from the intake clinics of 4 principals of each sub-centers. Additionally, we will recruit participants through other physicians and healthcare professionals. Those interested will contact the research assistant who will provide further information about the study objectives and procedures and will perform an initial eligibility screening interview by telephone.

2.4. Medical evaluation and enrolment procedure

Participants found to be eligible will be invited to attend a medical examination, to confirm the LET diagnosis and assess eligibility to participate in the research project.

Inclusion criteria

- Age ≥18 years old;
- Unilateral lateral elbow pain longer than 6 weeks duration;
- Pain over the lateral humeral epicondyle with pain severity of greater than 30 mm on a 100-mm visual analog scale (VAS), provoked by at least 2 of the following: gripping, palpation, resisted wrist or middle finger extension, or stretching of forearm extensor muscles with reduced pain-free grip;[16,49]
- Able to read and write in simplified Chinese (Mainland), understand and complete the questionnaire, and should provide informed consent.

Exclusion criteria

- Concomitant musculoskeletal pain conditions reported by participants to be their predominant complaint within the past 6 months;
- History of symptoms suggesting radicular, neurological, inflammatory or systemic arthritic conditions;
- Treatment by physiotherapy, electrophysical therapy, or injection within the past 6 months, or previous tennis elbow surgery;
- Contraindications to US, including dermatological conditions, abnormal sensation in the affected arm, indwelling electrical pumps/pacemakers, epilepsy, pregnancy or breastfeeding, et al.;
- Contraindications to CI, including hypertension, gastrointestinal ulcers, diabetes, mental illness, et al.

Following the medical evaluation, a research assistant will meet with the eligible participants and obtain written informed consent. Demographic variables will be reported before treatment (baseline) of all participants regarding age, sex, body mass index, affected elbow, dominant arm, lifestyle (smoking and drinking), and previous medical history. Participants will also be asked relevant questions about duration of

symptoms and previous treatments (rehabilitation exercises, injections or others). Others like occupation, employment characteristics (full-time or part-time work, manual or non-manual labor), employment status (whether on sickness absence), professional activity characteristics (repetitive movements for >4hours/day; wrist flexion for >2hours/day; elbow flexion and extension for >2hours/day; use of computer keyboard/ mouse [how many hours/day] and use of vibrating instruments for >2hours/day), and sports activities (how many hours/week, activity type, team or individual sports)[51] will be also collected.

2.5. Randomization and blinding

Participants will be randomized in three intervention groups (either US or CI or control arm) in a ratio of 1:1:1, using a computer-generated randomized sequence with varying unknown block sizes (either 3 or 6) for all study centers, without stratification. A research assistant with no involvement in the clinical care and evaluations of participants will prepare sequentially numbered, opaque, sealed envelopes according to the randomization lists, with security in place to ensure allocation data cannot be accessed or influenced by any person. At the appropriate time, this assistant will open the envelope and assure coordination of the therapeutic interventions.

The outcome assessor and statistician will be blinded to group allocation and not involved in treatment procedures.

2.6. Intervention

At the beginning, all participants will receive standardized education and advice on adjusting activity patterns and managing pain, which will be distributed in the form of printed brochures and orally assessed on their understanding of the content. Participants will be told that absolute rest of the arm will not be advocated, and activities that do not cause elbow pain should be encouraged. The primary physical impairment

in LET, which occurs in the muscle system, is best characterized as a deconditioning response of the forearm muscles to the pain. Therefore, all participants will receive the internationally best recommended fundamental intervention, EBT program, for the forearm muscles.[15] The EBT in this study will follow a standard protocol that has been adopted and used by several high-quality RCTs,[16,18,52,53] mainly for addressing motor impairments, relieving pain and stimulating tendon remodeling. 30 minutes per day, including basic tasks (pain free [1] gripping and [2] extension exercise) and appendage tasks ([3] flexion, [4] supination and pronation, and [5] radial and ulnar deviation exercise). Various kinds of resistance and load can be used, like free weights, rubber bands, manual resistance, isokinetic dynamometry or isometric contractions. [6] It is essential that all exercises that are performed for the upper limb must be done with sound alignment of the spine, trunk and proximal arm.

1) Pain-free gripping exercise with exercise putty, which allows practice of various different gripping actions.
2) Forearm extensor muscle exercise using a free-standing dumbbell. Note that the forearm is fully stabilized by the bench and upper body in sound postural alignment. Duration per repetition lasts about 6-10 s.
3) Dumbbell weight exercise for the forearm flexor muscle with 6-10 s per repetition. The postural is the same as 2).
4) Exercises for forearm supinator and pronator muscles using an imbalanced adjustable dumbbell weight with 6-10 s per repetition, from end range of supination to pronation with the participant maintaining full active control of the weight. The elbow bent to 90° with the arm stabilizing besides the trunk. Progressions in load imposed on the muscles can be achieved by increasing the weight or by increasing the distance between weight and hand.

5) Radial and ulnar deviation exercises are performed with similar equipment and guidelines in 4).

6) Education on recognition and correction of the poor posture from the pelvis to neck. Once the spine and trunk are aligned more optimally then the upper limb position should be addressed.

Participants in the [US group] will receive continuous mode US (Shanghai, China) at a frequency of 1 MHz and intensity of 1.0 W/cm^2 for 10 minutes in 5 days per week for 3 weeks on the maximum pain region of lateral elbow.

Participants allocated to the [CI group] will receive a single local infiltration of 1mL triamcinolone acetonide (10mg/ mL) and 1mL lidocaine 1%. Local corticosteroid injection was administered to the most painful area on pressure around the lateral epicondyle. Participants will be advised to wait for 20 min following injection, and to inform their doctor if there is any suggestion of infection or other adverse events. All adverse reactions will be managed by a committee chaired by the chief investigator. Rest from all strenuous activity for 1-2 weeks following injection will be strongly recommended, followed by gradual return to normal activities. Participants will be instructed to avoid aggressive return to activities even if substantial relief is obtained, to minimize potential recurrence of their symptoms.

Participants randomized to the [Control group] will neither receive US therapy nor corticosteroid injection. They will only receive the fundamental intervention, EBT program.

We discourage additional treatments to that assigned (that is, not per protocol) during the intervention period, but we allow the use of simple analgesics as needed. Participants will report all not per protocol treatments, such as drugs, in a diary.

2.7. Data management

Data will be collected during the participants' visits to the hospital at baseline, 3 weeks, 2 and 6 months, and one year after random assignment (**Table 1**). In order to maximize participant compliance in follow-up completion, reminder emails and a telephone call by the research assistant will be programmed. Registered participants will be withdrawn from the study if: (1) participant withdraws his/her consent, and (2) exclusion criteria is discovered after registration. The reason and date of discontinuation will be recorded. Consent to use the data already collected prior to a participant's withdrawal will be included in the consent form.

2.8. Outcome measures

Primary outcome

The primary outcome measure will be the difference in Patient-rated Tennis Elbow Evaluation (PRTEE). The PRTEE, formerly known as the Patient-Rated Forearm Evaluation Questionnaire, is a well validated composite scale measuring pain (5 items, with 0=no pain and 10=worst imaginable) and physical function (6 items for specific activities and 4 items for usual activities, with 0=no difficulty and 10=unable to do),[54] ranging from 0 to 100, with higher scores represent worse possible pain and more loss of function. The pain (intraclass correlation coefficients, ICC=0.89), physical function (ICC=0.83) and the total (ICC=0.89) scores all demonstrate excellent reliability.[55] A variation of 11/100 points or 37% of baseline scores are reported for clinical significance defined as "much better" or "completely recovered".[56] We use a validated Hong Kong Chinese version[57] of the PRTEE translated into simplified Chinese (Mainland) because the culture and language are the same.

Secondary outcome

Secondary outcome measures will be the differences in Visual Analogue Scale (VAS)[58] for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand

(Quick-DASH)[59] for upper limb disability, pain free/maximum grip strength, Work Limitations Questionnaire-25 (WLQ-25)[60] for functional limitations at work, EuroQol-5D (EQ-5D)[61] for life quality and health status, The Hospital Anxiety and Depression Scale (HADS)[62] for anxiety and depression status, Global Rating of Change (GROC) for treatment success and recurrence rate, and Mahomed scale[63] for participants' satisfaction.

■ Pain

The VAS will be used for pain evaluation, which consists of a 100-mm horizontal numbered line anchored at one end (0) with the words "no pain" and at the other end (100) with the words "worst pain imaginable", and whose score is determined by the distance between the left end of the line and the participant's mark in mm.[58] VAS is considered to be the most sensitive of all pain scoring scales and has been specifically validated in the LET population with high reliability (r=0.89) and a moderate correlation with pain-free grip strength (r=0.47).[64] Participants are asked to score their pain on this line during rest (at time of measure), provocation and maximum grip strength. The provocation test is conducted on the outpatient clinic by resisted dorsiflexion of the wrist during full elbow extension. Clinically relevant improvement will be defined when a 50% decrease in VAS is observed before and after the treatment.[65] The consumption of rescue medication taken by each patient will be also recorded at each follow-up visit.

■ Upper limb disability

The well-validated simplified Chinese (Mainland) version of Quick-DASH[66] will be used for elbow function evaluation, which consists of eleven questions scored on a 5-point scale similar to the DASH.[59] Total and individual module scores will be calculated out of 100, with a higher score indicating a worse status. A minimal clinically

important difference of 15.91 points has been reported.[67]

■ Grip strength

Pain free/maximum grip strength will be measured using a dynamometer (CAMRY, City of Industry, CA, USA). The participants will be asked to take a shoulder-width stance and allow their arms to hang loose, holding their arm adducted along the body and the elbow in full extension. The pain-free grip strength will be measured, followed by the measurement of the maximum grip strength, and the affected side will be measured first and then the unaffected side. The measurement readings will be not revealed to the subjects until the completion of the test. The pain-free grip strength will be measured up to the point when the subject slowly squeezes the dynamometer until the occurrence of pain. The maximum grip strength will be measured at the maximum grip level. The mean of three consecutive trials, separated by a 20s pause, will be calculated. Results will be presented as a ratio of values of the symptomatic side/ asymptomatic side×100.[68]

■ Functional limitations at work

In order to gather information that is complementary to the pain and disability scales, functional limitations at work will be measured with the WLQ-25. It contains 25 items arranged under four subscales addressing four dimensions of job demands, those are, time demands, physical demands, mental/interpersonal demands, and output demands.[60] A five-level ordinal response scale ranging from 0 (all of the time) to 4 (none of the time) with an additional sixth option (does not apply to my job) is used. The total scores range from 0-100 points, and a 13-point (out of 100) improvement for the summed score is established for clinically important differences.[69]

■ Life quality and health status

The EQ-5D is one of the widely validated generic health-related quality of life

(HRQol) measures known as its simplicity.[61] It contains a five-dimension descriptive system (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a VAS, ranging from 0 to 1, in which 1 represents perfect health. All the dimensions are grouped into three levels (no problem, some problem and extreme problem). We used a validated Chinese version[70] of the EQ-5D, which has been recommended by China Guidelines for Pharmacoeconomic Evaluations 2011 for a measure for HRQol and health utility.[71]

■ Anxiety and depression status

HADS will be used to identify and quantify two of the most common psychological disorders - anxiety and depression.[62] There is evidence of increased levels of anxiety and depression in people with LET.[72] HADS is a 14-item scale independent of somatic symptoms, which consists of two 7-item subscales measuring depression and anxiety respectively. A 4-point scale (from 0 representing absence of symptoms, to 3 representing maximum symptomatology) is used. The total scores for each subscale range from 0 to 21, with higher scores indicating higher levels of disorder. HADS has two cut offs for categorization: 0-7, "non-case"; 8-10, "possible or doubtful case"; 11-21, "probable or definite case".[73]

■ Treatment success and recurrence rate

Participants' treatment impression of change regarding their condition will be recorded on a 6-point Likert scale (from "completely recovered", "much improved", "somewhat improved", "same", "worse" to "much worse"). Success rates will be calculated by dichotomizing responses. Participants who report their overall condition as "completely recovered" or "much improved" since the beginning of the study will be counted as successes, while other responses will be counted as failures.[16,18] Recurrence will primarily be defined as occurring when a participant rates a success at

3 weeks and a failure at 2 or 6 months or one year on GROC.[16,18]

What's more, additional treatments after failure of management in this study (that is, not per protocol), if any, including subsequent interventions and even surgery, will be also recorded.

■ Participants' satisfaction

Similarly, participants' level of satisfaction on the evolution of their condition will be determined on a validated 4-point Likert scale ranging from "very satisfied", "somewhat satisfied", "somewhat dissatisfied" to "very dissatisfied".[74]

2.9. Adverse events

All adverse events, defined as any negative or unwanted reactions to intervention, will be recorded through the symptoms reported by the patients, and observations by a researcher at every visit. US treatment may cause mild local swelling, spot-like bleeding, ecchymosis, enhanced local pain response, and local hyperesthesia or decrease. CI-related adverse events are divided into acute and long-term ones. Acute events include dizziness, skin flushing, local bleeding, and someone may even develop rarer physical reactions, such as arrhythmias. Therefore, all participants must take at least 20 minutes in the outpatient room to observe and even manage any acute adverse reactions following the injection. Long-term events may cause skin pigmentation, local calcification and infection.

2.10. Sample size calculation

Sample size and power calculation are based on the primary outcome of PRTEE score. All sample size calculations assume two-sided analysis with a power of 90% (1-β=0.90) at a significant level of α=0.05. Based on previous trial, a standard deviation (SD) of 5.1-point on PRTEE score will be used.[75] To detect a minimum clinically significant difference of 11.0-point[56] (superiority margin) between US and control

groups (assuming a true difference of 15.6-point[43,75]), a total of 22 participants in each group is required. Allowing for an up to 10% drop out rate, we aim to enroll at least 24 participants in each group to complete the study.

2.11. Analysis plan

Baseline characteristics will be summarized for the three treatment groups using appropriate descriptive statistics. Both primary and secondary analysis will be conducted blind to treatment allocation and analyzed on intention-to-treat (ITT)[76] approach with all randomized participants retaining their original randomized group. Multiple imputation by chained equations will be used to address missing data caused by loss to follow-up and non-responses if these missing data are judged to be random.

The primary comparisons for PRTEE scores will be made using linear regression. In secondary analyses, repeated measures mixed model[77] will also be used to examine the associations between treatments and repeated outcome measures, with terms of treatment, time, trial center and corresponding baseline values as covariates (age, gender, body mass index, et al.). Linear regression will be used for numerical outcomes, and logistic/ordinal regression for any categorical outcomes.

2.12. Quality assurance/monitoring/management

A Manual of Operations and Procedures (MOP) and case report form will be developed as per protocol to standardize all procedures and staff training in areas such as patient recruitment, outcome measurement, data entry, management, analysis, and security, which also include the monitoring plans to assure patient protection and data integrity, thus facilitating consistency in protocol implementation and data collection. The investigators, physicians, research assistants, outcome assessors and statisticians are different people, and should receive Good Clinical Practice training. A trained

project manager will visit each center for monitoring to ensure data quality and compliance with trial protocol.

All data obtained will be kept strict and stored electronically on a database with secured and restricted access. An encryption will be used for data transfer, with removal for any information able to identify individuals. Data will be only deidentified for analysis at the completion of this study.

2.13. Study duration

Recruitment of the trial will begin in the November of 2021 and one-year follow-up for all participants is anticipated to be completed by March 2023. See **Table 1** for time points and recruitment progress.

2.14. Ethics and dissemination

The study has been approved by all 4 Medical Ethics Committees, those are, Ethics Committee of Shanghai Sixth People's Hospital (the leading clinical center, approval No. 2021-153), Ethics Committee of Shanghai East Hospital (LL-2021-KYHZ-003), Ethics Committee of Shanghai Tenth People's Hospital (SHSY-IEC-4.1/21-193/01), and Ethics Committee of Pudong New Area People's Hospital (IRBY2021-005). The potential risks of this clinical trial are considered to be minimal and are addressed in the protocol and consent forms. A written consent (**Supplementary 1**) will be obtained by clinical practitioners from each participant. The trial was registered on www.chictr.org website (registration number ChiCTR2100050547). Data will be published in peer-reviewed journals and presented at conferences, both nationally and internationally.

2.15. Limitation

This study will have one limitation. Participants and treating surgeons are inevitable not blinded, which may produce bias. However, we will strictly control the

outcome assessors and statisticians to be blinded to group allocation and not involved in treatment procedures to reduce the bias.

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Figure Legends

Figure 1 Participant flow chart

Table 1 Study evaluation procedures and timeline

Study procedure	Medical evaluation	Enrolment visit	3 weeks	2 months	6 months	One year
Determine eligibility	√	√				
Obtain signed consent		√				
Obtain medical and demographic data		√				
Give instructions for Pain medication diary		√				
Outcome measures						
Patient-Rated Tennis Elbow Evaluation		√	√	√	√	√
Visual Analogue Scale for pain		√	√	√	√	√
Shortened version of the Disabilities of the Arm, Shoulder and Hand questionnaire		√	√	√	√	√
Pain free/maximum grip strength		√	√	√	√	√
Work Limitations Questionnaire-25		√	√	√	√	√
EuroQol-5D		√	√	√	√	√
Hospital Anxiety and Depression Scale		√	√	√	√	√
Treatment success rate			√	√	√	√
Treatment recurrence rate				√	√	√
Participants' satisfaction			√	√	√	√

INDEX SECTION

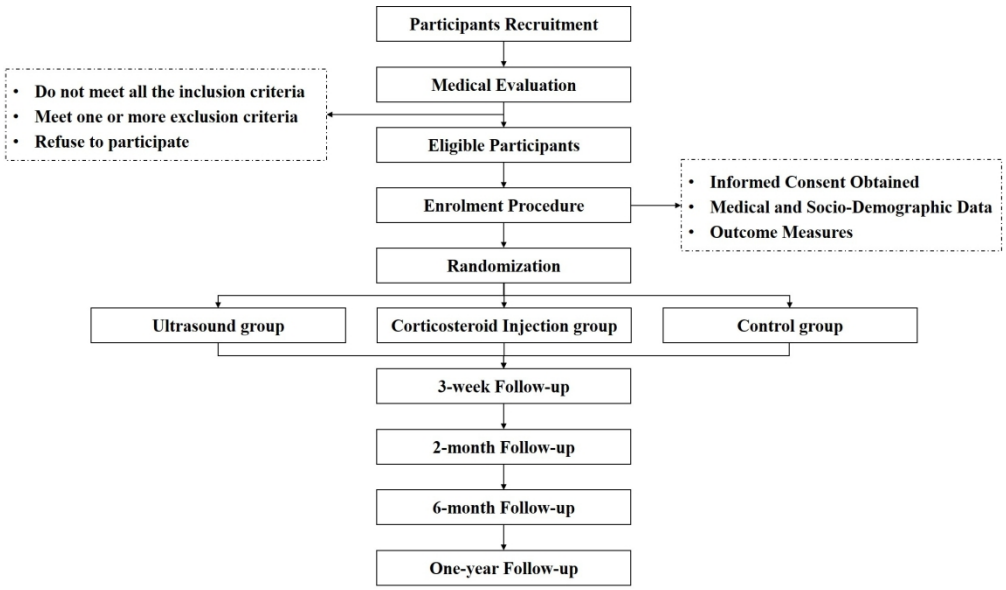

Figure 1/ Participant flow chart

365x212mm (150 x 150 DPI)

INFORMED CONSENT FORM

(English Version)

Participant Information Page

Study Title	:	Effectiveness of ultrasound therapy for the treatment of lateral elbow tendinopathy
Principal Investigator	:	Cunyi Fan
Sponsor	:	Shanghai Sixth People's Hospital

Dear participant:

You have been diagnosed with lateral elbow tendinopathy, and will be invited to participate in the study named "Effectiveness of ultrasound therapy for the treatment of lateral elbow tendinopathy". The study is conducted by the researchers themselves. Please read this informed consent carefully and make the decision whether to participate in this study or not. Participation in this study is entirely your choice. As a participant, you must give your written consent prior to joining the clinical study. When your doctor or researcher discusses informed consent with you, you can ask him or her to explain to you what you don't understand. We encourage you to discuss this thoroughly with your family and friends before making any decision to participate in this study. You have the right to refuse to participate in the study or withdraw from the study at any time without being penalized or losing your rights. If you are participating in another study, please inform your study doctor or investigator. The background, purpose, process and other important information of this study are as follows:

1. BACKGROUND

First described by Runge, lateral elbow tendinopathy (LET), also widely known as tennis elbow, has an estimated prevalence of 1% to 3% in the general population, and peaks at fourth and fifth decades of life, with an equal gender distribution. LET causes great burden on social economy, with an annual sickness absence rate as high as 5% in the working-aged adults. Though previously considered to be a "tendinitis", histological analysis suggests a degenerative rather than an inflammatory process in LET, which is now commonly converted to be considered as a "tendinosis". A LET diagnosis is usually straightforward, with clear clinical signs and symptoms. Patient most often complains of

pain at or around the bony surface of the upper half of the lateral epicondyle, and is likely to have a history of strenuous overuse relating to particular repetitive actions in the affected upper limb.

Though LET usually is a self-limiting condition, complaints may last up to 2 years or longer, therefore, it has great clinical value to find a better and faster recovery process. General principles of LET treatment should be orientated to pain relief, movement restoration, grip strength and endurance improvement, back to normal function and life quality, and control of further clinical deterioration. Treatments can be divided into operative and non-operative therapies. Invasive treatments commonly include open, arthroscopic and percutaneous release of the common extensor origin. Among these, Ultrasonic Percutaneous Tenotomy, a recent developed method, appealing to many researches for its good durability of pain relief and functional recovery, has a satisfied long-term (90 months) outcomes reported by Ang BFH. However, surgery is usually considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population; therefore, nonoperative treatment is suggested as first-line treatment. Generally, nonsurgical methods include injections (like corticosteroid, platelet-rich plasma, autologous blood, sodium hyaluronate, etc.), physiotherapy, extracorporeal shock-wave therapy (ESWT), ultrasound, topical glyceryl trinitrate, or oral naproxen, etc.

So far, despite the wide range of treatments; however, there is no successful and universally accepted regimen. In a cross-sectional survey of UK practice in managing LET, 81% experts recommended Exercise-based Therapy (EBT) as the first choice of intervention. EBT was also supported by high quality clinical trials and systematic reviews, regarding as the most cost-effective treatment for LET. The survey also showed that, as the mainstream treatment for a long time, corticosteroid injection (CI) was still the most recommended intervention second to EBT, due to its quick pain relief and physical functional improvement, though the recurrence rate may be high and prognosis may be worsened in the long term. In additional, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hyaluronate injection, platelet-rich plasma injection, ESWT and acupuncture still remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. US can reduce muscle spasms and pain, and facilitate tissue repair by increasing local blood flow and stimulating inflammatory mediators. US has been widely reported to be treatment beneficial in fracture nonunions, osteoarthritis, chronic muscle pain, soft tissue injury, etc. As for tendinopathy, US is also reported to be a potential

noninvasive treatment modality for frozen shoulder, rotator cuff, achilles and patellar tendinopathy. Some studies have reported the efficacy of US in LET treatment, but with low grade of study design and data, and most of them focused on the comparison between US and ESWT. Both Yalvaç B and Özmen T have shown significant improvements in terms of pain, upper limb function, strength and life quality from baseline after treatment with US. However, they did not have a control group, which would make it unclear whether the efficacy come from US itself or passing time, as LET is a self-limited disease.

Therefore, the role of US in LET treatment still needs to be further explored by high-quality study. Additionally, to our best of knowledge, no study has compared the efficacy between US and CI in LET treatment yet.

2. STUDY PURPOSE

The purpose of the current three-arm, prospective, randomized, multicenter trial is to investigate the effectiveness of US in treatment for LET, that is, US versus CI versus control, with a fundamental intervention of EBT, on clinical and functional outcomes, including Patient-Rated Tennis Elbow Evaluation (PRTEE).

3. STUDY PROCESS

(1) How many people will participate in the study?

About 72 people will participate in the study at 4 municipal tertiary hospitals: Shanghai Sixth People's Hospital (leader unit), Shanghai East Hospital (participating unit), Shanghai Tenth People's Hospital (participating unit) and Pudong New Area People's Hospital of Shanghai (participating unit).

(2) What are the study procedures?

Before you are enrolled in the study, your medical history will be asked, and you will be screened for lateral elbow tendinopathy with a lateral elbow irritation test.

After determining that you are eligible to participate in the study based on inclusion and exclusion criteria, you will be collected and randomly assigned to treatment:

A. Characteristic features collection

You will be asked for your age, sex, body mass index, affected elbow, dominant arm, lifestyle (smoking and drinking), and previous medical history. As well as relevant questions about duration of symptoms and previous treatments (rehabilitation exercises, injections or others). Others like occupation, employment characteristics (full-time or part-

time work, manual or non-manual labor), employment status (whether on sickness absence), professional activity characteristics, and sports activities will be also collected.

B. Clinical features collection

You will complete the following questionnaires, including Patient-Rated Tennis Elbow Evaluation (PRTEE) for elbow function and symptom, Visual Analogue Scale (VAS) for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand (Quick-DASH) for upper limb disability, pain free/maximum grip strength, Work Limitations Questionnaire-25 (WLQ-25) for functional limitations at work, EuroQol-5D (EQ-5D) for general health, Hospital Anxiety and Depression Scale (HADS) for mental status, Global Rating of Change for treatment success and recurrence rate, and Mahomed scale for participant's satisfaction.

C. Treatment by group

At the beginning, all of you will receive standardized education and advice on adjusting activity patterns and managing pain, which will be distributed in the form of printed brochures and orally assessed on their understanding of the content. You will be told that absolute rest of the arm will not be advocated, and activities that do not cause elbow pain should be encouraged. The primary physical impairment in LET, which occurs in the muscle system, is best characterized as a deconditioning response of the forearm muscles to the pain. Therefore, all of you will receive the internationally best recommended fundamental intervention, EBT program, for the forearm muscles. The EBT in this study will follow a standard protocol that has been adopted and used by several high-quality RCTs, mainly for addressing motor impairments, relieving pain and stimulating tendon remodeling. 30 minutes per day, including basic tasks (pain free [1] gripping and [2] extension exercise) and appendage tasks ([3] flexion, [4] supination and pronation, and [5] radial and ulnar deviation exercise). Various kinds of resistance and load can be used, like free weights, rubber bands, manual resistance, isokinetic dynamometry or isometric contractions. [6] It is essential that all exercises that are performed for the upper limb must be done with sound alignment of the spine, trunk and proximal arm.

You will be randomly assigned to one of three groups, [US group] vs. [CI group] vs. [Control group]:

(a) If you are assigned in the [US group], you will receive continuous mode US (Shanghai, China) at a frequency of 1 MHz and intensity of 1.0 W/cm^2 for 10 minutes in 5 days per week for 3 weeks on the maximum pain region of lateral elbow.

(b) If you are allocated to the [CI group], you will receive a single local infiltration of 1mL triamcinolone acetonide (10mg/ mL) and 1mL lidocaine 1%. Local corticosteroid injection was administered to the most painful area on pressure around the lateral

epicondyle. Participants will be advised to wait for 20 min following injection, and to inform their doctor if there is any suggestion of infection or other adverse events. All adverse reactions will be managed by a committee chaired by the chief investigator. Rest from all strenuous activity for 1-2 weeks following injection will be strongly recommended, followed by gradual return to normal activities. Participants will be instructed to avoid aggressive return to activities even if substantial relief is obtained, to minimize potential recurrence of their symptoms.

(c) If you are randomized to the [Control group], you will neither receive US therapy nor corticosteroid injection. They will only receive the fundamental intervention, EBT program.

We discourage additional treatments to that assigned (that is, not per protocol) during the intervention period, but we allowed the use of simple analgesics as needed. You will report all not per protocol treatments, such as drugs, in a diary.

D. Follow-up features collection

Follow-up data will be collected during your visits to the hospital at 3 weeks, 2 and 6 months, and one year after random assignment.

(3) How long will the study last?

This study will continue for 1 year from the time you receive treatment, and we will collect follow-up information from you at 3 weeks, 2 months, 6 months, and one year at your regular outpatient review.

You may drop out of the study at any time without losing any benefits to which you are entitled. However, if you decide to withdraw during the study, you are encouraged to talk to your doctor first. If you experience a serious adverse event, or if your study doctor feels it is not in your best interest to continue in the study, he or she may decide to withdraw you from the study. The sponsor or regulatory agency may also terminate during the study period. However, your withdrawal will not affect your normal medical treatment and rights.

If you withdraw from the study for any reason, you may be asked about your participation in the study. You may also be asked for a medical examination and follow-up questionnaire if your doctor deems it necessary.

(4) Information and biological specimens collected during the study

Biological specimens are not involved in this study, and the information collected is basic characteristics features, preoperative and follow-up clinical features (see the study procedures for details).

All data obtained will be kept strict and stored electronically on a database with

secured and restricted access. An encryption will be used for data transfer, with removal for any information able to identify individuals. Data will be only deidentified for analysis at the completion of this study.

4. RISKS AND BENEFITS

(1) What are the risks of participating in this study?

The risks you may incur by participating in this study are as follows. You should discuss these risks with your study doctor or, if you prefer, with your regular care provider.

US treatment may cause mild local swelling, spot-like bleeding, ecchymosis, enhanced local pain response, and local hyperesthesia or decrease. The occurrence of these reactions depends on the dose of treatment, the extent of the lesion, and the individual patient, and usually does not require special treatment. Severe adverse reactions can be treated locally, or prolong the interval of treatment, reduce the intensity of treatment. If the treatment does not improve or abnormal conditions occur, the treatment should be stopped and immediately go to the hospital.

CI-related adverse events are divided into acute and long-term ones. Acute events include dizziness, skin flushing, local bleeding, and someone may even develop rarer physical reactions, such as arrhythmias. The occurrence of these reactions depends on the individual patient, and usually does not require special treatment. In addition, during the injection, there may be a slight tingling sensation due to tissue and nerve damage in the skin. If the patient is physically sensitive, the pain may be more intense. Someone may even develop rarer physical reactions, such as arrhythmias. Therefore, all participants must take at least 20 minutes in the outpatient room to observe and even manage any acute adverse reactions following the injection. Long-term events may cause skin pigmentation, local calcification and infection. The drugs in the CI contain hormones, therefore, if are injected repeatedly and for a long time, it will cause damage to the tissues in the skin, so local calcification and skin stiffness occur. If the drug penetrates the bones, it can cause osteoporosis. After the injection, if the patient's physical condition decreases, and the wound is not kept clean, it may lead to bacterial invasion of the wound, so the wound healing speed will be slow, and there will develop infection and inflammation. These adverse reactions can be avoided by reducing the number of CIs and standardizing injection procedures.

EBT is exercise, and theoretically there are no complications.

If you experience any discomfort, new changes, or any unexpected conditions during the study period, whether or not related to the study, you should inform your doctor in a

timely manner, and he/she will judge and administer appropriate medical treatment.

During the study period, you need to visit the hospital on time and do some examinations, which will take up some of your time and may cause trouble or inconvenience to you.

(2) What are the benefits of participating in the study?

If you agree to participate in this study, you may receive direct medical benefits, such as accelerated relief of symptoms of LET. You can also have a deeper understanding of diseases and so on. In addition, we hope that the information gained from your participation in this study will benefit you or other patients with similar conditions in the future.

5. ALTERNATIVE TREATMENT OPTIONS

In addition to participating in this study, you may receive the other treatments provided by your doctor: corticosteroid injection, EBT, autologous blood or hyaluronate injection, platelet-rich plasma injection, ESWT, acupuncture, and surgery, etc.

Please discuss these and other possible options with your doctor.

Treatments can be divided into operative and non-operative therapies. Invasive treatments commonly include open, arthroscopic and percutaneous release of the common extensor origin. Among these, Ultrasonic Percutaneous Tenotomy, a recent developed method, appealing to many researches for its good durability of pain relief and functional recovery, has a satisfied long-term (90 months) outcomes reported by Ang BFH. However, surgery is usually considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population; therefore, nonoperative treatment is suggested as first-line treatment. Generally, nonsurgical methods include injections (like corticosteroid, platelet-rich plasma, autologous blood, sodium hyaluronate, etc.), physiotherapy, extracorporeal shock-wave therapy (ESWT), ultrasound, topical glyceryl trinitrate, or oral naproxen, etc.

So far, despite the wide range of treatments; however, there is no successful and universally accepted regimen. In a cross-sectional survey of UK practice in managing LET, 81% experts recommended Exercise-based Therapy (EBT) as the first choice of intervention. EBT was also supported by high quality clinical trials and systematic reviews, regarding as the most cost-effective treatment for LET. The survey also showed that, as the mainstream treatment for a long time, corticosteroid injection (CI) was still the most recommended intervention second to EBT, due to its quick pain relief and physical functional improvement, though the recurrence rate may be high and prognosis may be

worsened in the long term. In additional, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hyaluronate injection, platelet-rich plasma injection, ESWT and acupuncture still remain controversial or provide little to no benefit.

6. USE OF RESEACH RESULTS AND CONFIDENTIALITY OF PERSONAL INFORMATION

Results conducted through this program may be published in medical journals with the understanding and assistance of you and other participants, but we will keep your study records confidential as required by law.

The personal information of study participants will be kept strictly confidential, and your personal information will not be disclosed unless required by relevant laws.

If necessary, government administrative departments, hospital ethics committees and other relevant researchers can access your data according to regulations.

7. RESEARCH EXPENSES AND RELATED COPENSATION

(1) Cost of drugs/instruments used in the study and related examinations

There are no potential additional costs for this study. Routine outpatient fees include registration, examination for LET, oral non-steroidal anti-inflammatory drugs, etc. There is no cost involved in EBT. The expenses related to US and CI injection will be borne by our research group and funding. In addition, you will be solely responsible for the expenses incurred by you for any treatment other than this study, as well as for the routine treatment and examination required for any concurrent disease.

(2) Compensation for participation in the study

There are no additional compensation costs for this study.

(3) Compensation/compensation after damage

For participants who suffer damage related to this study, the sponsor Shanghai Sixth People's Hospital will bear the treatment cost and corresponding economic compensation in accordance with Chinese laws and regulations.

8. RIGHTS OF PARTICIPANTS AND RELEVANT MATTERS NEEDING

ATTENTION

(1) Your rights

Your participation in the study is voluntary throughout the entire process.

If you decide not to participate in this study, it will not affect other treatments you should receive.

If you decide to participate, you will be asked to sign this written informed consent. You have the right to withdraw from the trial at any stage without discrimination or unfair treatment, and your medical treatment and rights will not be affected.

(2) Matters needing attention

As a subject, you are required to provide true information about your medical history and current medical condition;

Inform the study doctor of any discomfort observed during the study;

Do not take any restricted drugs, food, etc. as advised by your doctor;

Tell the study doctor if you have recently participated in or are currently participating in other studies.

During the intervention, we discouraged additional therapy (i.e., not according to the grouping protocol), but we permitted the use of analgesics when needed (only acetaminophen and NSAIDs).

For medications taken, the name, dose, frequency and duration will be recorded at all follow-up visits.

9. RELEVANT CONTACT INFORMATION

If there is any significant new information during the study that may affect your willingness to continue to participate, your doctor will inform you promptly. If you are interested in your own study data, or you would like to know the findings after this study, you may ask any questions about this study at any time and receive answers accordingly, Please contact doctor Ziyang Sun at **********.

Participant Signature Page

Informed Consent Statement:

I have been informed of the purpose, background, process, risks and benefits of this study. I have plenty of time and opportunity to ask questions, and I am satisfied with the answers.

I am also told who to contact when I have questions, want to report difficulties, concerns, suggestions for research, or want further information, or to help with research.

I have read this informed consent and agree to participate in this study.

I understand that I may choose not to participate in the study or withdraw from the study at any time during the study without any reason.

I already know that if I get worse, or if I have a serious adverse event, or if my study doctor decides it's not in my best interest to continue, he or she will decide to withdraw me from the study. The funder or regulatory agency may terminate during the study without my consent. If this happens, the doctor will inform me and the study doctor will discuss other options with me.

I will be provided with a copy of the informed consent which contains my signature and that of the investigator.

Participant Signature: _____

Date: _____

(NOTE: If participant has no capacity/limited capacity, legal representative signature and date will be required)

Legal Representative's Signature: _____

Date: _____

Investigator Signature: _____

Date: _____

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
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Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4/6
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	2
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2/3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	2/3

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-10
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	8-10
Objectives	#7	Specific objectives or hypotheses	10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	11-12

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-15
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Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-15
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-20
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	22

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20-21
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-16, 21-22
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15-16, 21-22
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	15-16, 21-22

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15-16, 21-22
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16, 21-22
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	20

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	22
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	22
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22
Declaration of	#28	Financial and other competing interests for principal	22

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20-22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	21-22
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21-22
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21-22
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21-22
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Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	22
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BMJ Open

Efficacy of ultrasound therapy for the treatment of lateral elbow tendinopathy (the UCICLET trial): study protocol for a three-arm, prospective, multicenter, randomised controlled trial

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TITLE PAGE

Title

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Author Contributions

SZY and CS are the primary investigators.

SZY, CS, LWX, ZYY, FCY participated in the development of the study design.

SZY, CS, LWX, SGX, LJJ, WJ, WW, ZYY, and FCY participated in the study conduct.

SZY, CS and LWX drafted the manuscript under FCY's supervision.

FCY contributed to applying for and gaining funding.

All authors contributed to the content and critical revision and approved the final draft of the manuscript.

Conflict of interests

The authors, their immediate families, and any research foundation with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

The authors declare no competing financial interests.

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ETHICS

The study has been approved by all 4 Medical Ethics Committees, those are, Ethics Committee of Shanghai Sixth People's Hospital (the leading clinical center, approval No. 2021-153), Ethics Committee of Shanghai East Hospital (EC.D(BG).016.03.1-2021-096), Ethics Committee of Shanghai Tenth People's Hospital (SHSY-IEC-4.1/21-193/01), and Ethics Committee of Pudong New Area People's Hospital (IRBY2021-005). The research registry number is ChiCTR2100050547 at http://www.chictr.org.cn. Data will be analyzed anonymously; all patients will approve the results of this study by written consent. The written consent approval will be documented in the patients' files. All clinical investigations will be conducted in accordance with the guidelines of the Declaration of Helsinki.

ABSTRACT

Introduction

Lateral elbow tendinopathy (LET) is a highly prevalent disease among the middle-aged population, with no consensus on optimal management. Nonoperative treatment is generally accepted as the first-line intervention. Ultrasound (US) therapy has been reported to be beneficial for various orthopedics diseases, including tendinopathy. The purpose of this study is to investigate the efficacy of US for LET treatment.

Methods and analysis

This protocol entails a three-arm, prospective, multicenter, randomised controlled trial. Seventy-two eligible participants with clinically confirmed LET will be assigned to either (1) US, (2) Corticosteroid Injections or (3) control group. All participants will receive Exercise-based Therapy as a fundamental intervention. The primary outcome is Patient-Rated Tennis Elbow Evaluation. The secondary outcomes include Visual Analogue Scale for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand for upper limb disability, pain free/maximum grip strength, Work Limitations Questionnaire-25 for functional limitations at work, EuroQol-5D for general health, Hospital Anxiety and Depression Scale for mental status, Global Rating of Change for treatment success and recurrence rate, and Mahomed scale for participant's satisfaction. Adverse events will be recorded. Intention-to-treat analyses will be used.

Ethics and dissemination

Ethics Committees of all clinical centers have approved this study. The leading center is Shanghai Sixth People's Hospital, whose approval number is 2021-153. New versions with appropriate amendments will be submitted to the committee for further approval. Study results will be published in peer-reviewed journals and presented at local, national and international conferences.

Trial registration number

ChiCTR2100050547.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Exercise-based Therapy as a fundamental intervention for all participants.
- The first randomised controlled trial (RCT) to compare the efficacy between ultrasound therapy and corticosteroid injections in lateral elbow tendinopathy treatment.
- Multicenter RCT with blinded outcome assessor and statistician.
- Use of several patient-reported outcome measures as well as objective parameters.
- Participants and treating surgeons not blinded.

1. INTRODUCTION

First described by Runge,[1] lateral elbow tendinopathy (LET), also widely known as tennis elbow, has an estimated prevalence of 1% to 3% in the general population, and peaks at fourth and fifth decades of life, with an equal gender distribution.[2] LET causes a great burden on the social economy, with an annual sickness absence rate as high as 5% in the working-aged adults.[3] Though previously considered as a "tendinitis", histological analysis suggests a degenerative rather than an inflammatory process in LET, which is now commonly converted to be considered as a "tendinosis".[4] A LET diagnosis is usually straightforward, with clear clinical signs and symptoms. The patient most often complains of pain at or around the bony surface of the upper half of the lateral epicondyle and is likely to have a history of strenuous overuse relating to particular repetitive actions in the affected upper limb.[5,6]

Though LET usually is a self-limiting condition, complaints may last up to 2 years or longer,[7] therefore, it has great clinical value to find a better and faster recovery process. General principles of LET treatment should be orientated to pain relief, movement restoration, grip strength and endurance improvement, back to normal function and life quality, and control of further clinical deterioration.[8] Treatments can be divided into operative and non-operative therapies. Invasive treatments commonly include open, arthroscopic and percutaneous release of the common extensor origin.[9] Among these, Ultrasonic Percutaneous Tenotomy, a recently developed method, appealing to many researchers for its good durability of pain relief and functional recovery,[10] has satisfactory long-term (90 months) outcomes reported by Ang BFH.[11] However, surgery is usually considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population;[2] therefore, nonoperative treatment is suggested as first-

line treatment.[12] Generally, nonsurgical methods include injections (like corticosteroid, platelet-rich plasma, autologous blood, sodium hyaluronate, etc.), physiotherapy, extracorporeal shock-wave therapy (ESWT), ultrasound, topical glyceryl trinitrate, or oral naproxen, etc.[13,14]

So far, despite the wide range of treatments, there is no successful and universally accepted regimen. In a cross-sectional survey of UK practice in managing LET, 81% of experts recommended Exercise-based Therapy (EBT) as the first choice of intervention.[15] EBT was also supported by high-quality clinical trials[16-18] and systematic reviews[19,20], regarded as the most cost-effective treatment for LET.[21] The survey also showed that, as the mainstream treatment for a long time, corticosteroid injection (CI) was still the most recommended intervention second to EBT,[15] due to its quick pain relief and physical functional improvement, though the recurrence rate may be high and prognosis may be worsened in the long term.[16-18] In addition, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hyaluronate injection,[22] platelet-rich plasma injection,[23] ESWT[24] and acupuncture[25] remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. US can reduce muscle spasms and pain, and facilitate tissue repair by increasing local blood flow and stimulating inflammatory mediators.[26] US has been widely reported to be treatment beneficial in fracture nonunions,[27,28] osteoarthritis,[29,30] chronic muscle pain,[31,32] soft tissue injury,[33] etc. As for tendinopathy, US is also a potential noninvasive treatment modality for frozen shoulder,[34,35] rotator cuff,[36] achilles[37,38] and patellar[39] tendinopathy. Some studies have reported the efficacy of US in LET treatment, but with low grade of study design and data,[40] and most of them focused on the comparison between US and ESWT[41-45]. Both Yalvaç B[43] and Özmen

T[41] have shown significant improvements in pain, upper limb function, strength and life quality from baseline after treatment with US. However, they did not have a control group, which would make it unclear whether the efficacy comes from US itself or the passing time, as LET is a self-limited disease. Therefore, the role of US in LET treatment still needs to be further explored by high-quality studies. Additionally, to our best knowledge, no study has compared the efficacy between US and CI in LET treatment yet.

Therefore, the purpose of the current three-arm, prospective, randomized, multicenter trial is to investigate the efficacy of US in treatment for LET, that is, US versus CI versus control, with a fundamental intervention of EBT, on clinical and functional outcomes, including Patient-Rated Tennis Elbow Evaluation (PRTEE). In view of recent literatures, CI should be discouraged in LET;[22,46] however, it's still common in clinics due to the ability to satisfy patient's need for quick pain relief.[15] Thus, a change in the paradigm of LET treatment is necessary. This change will come about through proposed evidence-based treatment guidelines. There have been some ongoing clinical trials on LET treatment in recent years,[47-49] and our prospective RCT proposes to complement and add to this relevant and much needed scientific effort.

2. METHODS

2.1. Study design

The design of this study is a three-arm, prospective, multicenter, randomised controlled trial that will enroll participants with a diagnosis of chronic symptomatic LET from 4 municipal tertiary hospitals (Shanghai Sixth People's Hospital, Shanghai East Hospital, Shanghai Tenth People's Hospital, and Pudong New Area People′s Hospital of Shanghai). This manuscript is written according to the SPIRIT guidelines.[50]

2.2. Participant and public involvement

This study was done without participant involvement. Participants were not invited to comment on the design and were not consulted to develop patient-relevant outcomes. Participants will not be invited to contribute to the writing or editing of this manuscript for readability or accuracy. The resulting publications will be disseminated to the public via mass media. Participants as a whole will be acknowledged at the end of our publications and presentations.

2.3. Participant recruitment

Figure 1 shows the participant flow chart throughout the study. Participants will be recruited over a period of 5 months, from the intake clinics of 4 principals of each sub-centers. Additionally, we will recruit participants through other physicians and healthcare professionals. Those interested will contact the research assistant who will provide further information about the study objectives and procedures and will perform an initial eligibility screening interview by telephone.

2.4. Medical evaluation and enrolment procedure

Participants potentially eligible will be invited to attend a medical examination to confirm the LET diagnosis and assess eligibility to participate in the research project.

Inclusion criteria

- Age ≥18 years old;
- Unilateral lateral elbow pain longer than 6 weeks duration;
- Pain over the lateral humeral epicondyle with pain severity of greater than 30 mm on a 100-mm visual analog scale (VAS), provoked by at least 2 of the following: gripping, palpation, resisted wrist or middle finger extension, or stretching of forearm extensor muscles with reduced pain-free grip;[16,49]
- Able to read and write in simplified Chinese (Mainland), understand and complete the questionnaire, and provide informed consent.

Exclusion criteria

- Concomitant musculoskeletal pain conditions reported by participants to be their predominant complaint within the past 6 months;
- History of symptoms suggesting radicular, neurological, inflammatory or systemic arthritic conditions;
- Treatment by physiotherapy, electrophysical therapy, or injection within the past 6 months, or previous tennis elbow surgery;
- Contraindications to US, including dermatological conditions, abnormal sensation in the affected arm, indwelling electrical pumps/pacemakers, epilepsy, pregnancy or breastfeeding, et al.;
- Contraindications to CI, including hypertension, gastrointestinal ulcers, diabetes, mental illness, et al.

Following the medical evaluation, a research assistant will meet with the eligible participants and obtain written informed consent. Demographic variables will be reported before treatment (baseline) of all participants regarding age, sex, body mass index, affected elbow, dominant arm, lifestyle (smoking and drinking), and previous medical history. Participants will also be asked relevant questions about the duration of

symptoms and previous treatments (rehabilitation exercises, injections or others). Others like occupation, employment characteristics (full-time or part-time work, manual or non-manual labor), employment status (whether on sickness absence), professional activity characteristics (repetitive movements for >4hours/day; wrist flexion for >2hours/day; elbow flexion and extension for >2hours/day; use of computer keyboard/ mouse [how many hours/day] and use of vibrating instruments for >2hours/day), and sports activities (how many hours/week, activity type, team or individual sports)[51] will also be collected.

2.5. Randomization and blinding

Participants will be randomized in three intervention groups (either US or CI or control arm) in a ratio of 1:1:1, using a computer-generated randomized sequence with varying unknown block sizes (either 3 or 6) for all study centers, without stratification. A research assistant with no involvement in the clinical care and evaluations of participants will prepare sequentially numbered, opaque, sealed envelopes according to the randomization lists, with security in place to ensure allocation data cannot be accessed or influenced by any person. At the appropriate time, this assistant will open the envelope and assure coordination of the therapeutic interventions.

The outcome assessor and statistician will be blinded to group allocation and not involved in treatment procedures.

2.6. Intervention

At the beginning, all participants will receive standardized education and advice on adjusting activity patterns and managing pain, which will be distributed in the form of printed brochures and orally assessed on their understanding of the content. Participants will be told that the absolute rest of the arm will not be advocated, and activities that do not cause elbow pain should be encouraged. The primary physical

impairment in LET, which occurs in the muscle system, is best characterized as a deconditioning response of the forearm muscles to the pain. Therefore, all participants will receive the internationally best recommended fundamental intervention, EBT program, for the forearm muscles.[15] The EBT in this study will follow a standard protocol that has been adopted and used by several high-quality RCTs,[16,18,52,53] mainly for addressing motor impairments, relieving pain and stimulating tendon remodeling. Thirty minutes per day, including basic tasks (pain-free [1] gripping and [2] extension exercise) and appendage tasks ([3] flexion, [4] supination and pronation, and [5] radial and ulnar deviation exercise). Various kinds of resistance and load can be used, like free weights, rubber bands, manual resistance, isokinetic dynamometry or isometric contractions. [6] It is essential that all exercises performed for the upper limb be done with sound alignment of the spine, trunk, and proximal arm.

1) Pain-free gripping exercise with exercise putty, which allows practice of various gripping actions.
2) Forearm extensor muscle exercise using a free-standing dumbbell. Note that the forearm is fully stabilized by the bench and upper body in sound postural alignment. Duration per repetition lasts about 6-10 s.
3) Dumbbell weight exercise for the forearm flexor muscle with 6-10 s per repetition. The postural is the same as 2).
4) Exercises for forearm supinator and pronator muscles using an imbalanced adjustable dumbbell weight with 6-10 s per repetition, from end range of supination to pronation with the participant maintaining full active control of the weight. The elbow bent to 90° with the arm stabilizing beside the trunk. Progressions in load imposed on the muscles can be achieved by increasing the weight or the distance between weight and hand.

5) Radial and ulnar deviation exercises are performed with similar equipment and guidelines in 4).

6) Education on recognition and correction of the poor posture from the pelvis to neck. Once the spine and trunk are aligned more optimally, the upper limb position should be addressed.

Participants in the [US group] will receive continuous mode US (Shanghai, China) at a frequency of 1 MHz and intensity of 1.0 W/cm^2 for 10 minutes in 5 days per week for 3 weeks on the maximum pain region of the lateral elbow.

Participants allocated to the [CI group] will receive a single local infiltration of 1mL triamcinolone acetonide (10mg/ mL) and 1mL lidocaine 1%. Local corticosteroid injection was administered to the most painful area on pressure around the lateral epicondyle. Participants will be advised to wait for 20 min following injection and inform their doctor if there is any suggestion of infection or other adverse events. All adverse reactions will be managed by a committee chaired by the chief investigator. Rest from all strenuous activity for 1-2 weeks following injection will be strongly recommended, followed by a gradual return to normal activities. Participants will be instructed to avoid an aggressive return to activities even if substantial relief is obtained to minimize the potential recurrence of their symptoms.

Participants randomized to the [Control group] will neither receive US therapy nor corticosteroid injection. They will only receive the fundamental intervention, EBT program.

We discourage additional treatments to that assigned (that is, not per protocol) during the intervention period, but we allow the use of simple analgesics as needed. Participants will report all not per protocol treatments, such as drugs, in a diary.

2.7. Data management

Data will be collected during the participants' visits to the hospital at baseline, 3 weeks, 2 and 6 months, and one year after random assignment (**Table 1**). In order to maximize participant compliance in follow-up completion, reminder emails and a telephone call by the research assistant will be programmed. Registered participants will be withdrawn from the study if: (1) participant withdraws his/her consent, and (2) exclusion criteria is discovered after registration. The reason and date of discontinuation will be recorded. Consent to use the data already collected prior to a participant's withdrawal will be included in the consent form.

2.8. Outcome measures

Primary outcome

The primary outcome measure will be the difference in Patient-rated Tennis Elbow Evaluation (PRTEE). The PRTEE, formerly known as the Patient-Rated Forearm Evaluation Questionnaire, is a well-validated composite scale measuring pain (5 items, with 0=no pain and 10=worst imaginable) and physical function (6 items for specific activities and 4 items for usual activities, with 0=no difficulty and 10=unable to do),[54] ranging from 0 to 100, with higher scores represent worse possible pain and more loss of function. The pain (intraclass correlation coefficients, ICC=0.89), physical function (ICC=0.83) and the total (ICC=0.89) scores all demonstrate excellent reliability.[55] A variation of 11/100 points or 37% of baseline scores are reported for clinical significance defined as "much better" or "completely recovered".[56] We use a validated Hong Kong Chinese version[57] of the PRTEE translated into simplified Chinese (Mainland) because the culture and language are the same.

Secondary outcome

Secondary outcome measures will be the differences in Visual Analogue Scale (VAS)[58] for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand

(Quick-DASH)[59] for upper limb disability, pain free/maximum grip strength, Work Limitations Questionnaire-25 (WLQ-25)[60] for functional limitations at work, EuroQol-5D (EQ-5D)[61] for life quality and health status, The Hospital Anxiety and Depression Scale (HADS)[62] for anxiety and depression status, Global Rating of Change (GROC) for treatment success and recurrence rate, and Mahomed scale[63] for participants' satisfaction.

■ Pain

The VAS will be used for pain evaluation, which consists of a 100-mm horizontal numbered line anchored at one end (0) with the words "no pain" and at the other end (100) with the words "worst pain imaginable". The score is determined by the distance between the left end of the line and the participant's mark in mm.[58] VAS is considered to be the most sensitive of all pain scoring scales and has been specifically validated in the LET population with high reliability (r=0.89) and a moderate correlation with pain-free grip strength (r=0.47).[64] Participants are asked to score their pain on this line during rest (at time of measure), provocation and maximum grip strength. The provocation test is conducted on the outpatient clinic by resisted wrist dorsiflexion during full elbow extension. Clinically relevant improvement will be defined when a 50% decrease in VAS is observed before and after the treatment.[65] The consumption of rescue medication taken by each patient will be also recorded at each follow-up visit.

■ Upper limb disability

The well-validated simplified Chinese (Mainland) version of Quick-DASH[66] will be used for elbow function evaluation, consisting of eleven questions scored on a 5-point scale similar to the DASH.[59] Total and individual module scores will be calculated out of 100, with a higher score indicating a worse status. A minimal clinically important difference of 15.91 points has been reported.[67]

■ Grip strength

Pain free/maximum grip strength will be measured using a dynamometer (CAMRY, City of Industry, CA, USA). The participants will be asked to take a shoulder-width stance and allow their arms to hang loose, holding their arm adducted along the body and the elbow in full extension. The pain-free grip strength will be measured, followed by the maximum grip strength, and the affected side will be measured first and then the unaffected side. The measurement readings will be not revealed to the subjects until the completion of the test. The pain-free grip strength will be measured up to the point when the subject slowly squeezes the dynamometer until the occurrence of pain. The maximum grip strength will be measured at the maximum grip level. The mean of three consecutive trials, separated by a 20s pause, will be calculated. Results will be presented as a ratio of values of the symptomatic side/ asymptomatic side×100.[68]

■ Functional limitations at work

In order to gather the information that is complementary to the pain and disability scales, functional limitations at work will be measured with the WLQ-25. It contains 25 items arranged under four subscales addressing four dimensions of job demands: time demands, physical demands, mental/interpersonal demands, and output demands.[60] A five-level ordinal response scale ranging from 0 (all of the time) to 4 (none of the time) with an additional sixth option (does not apply to my job) is used. The total scores range from 0-100 points, and a 13-point (out of 100) improvement for the summed score is established for clinically important differences.[69]

■ Life quality and health status

The EQ-5D is a widely validated generic health-related quality of life (HRQol) measure known for its simplicity.[61] It contains a five-dimension descriptive system

(mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a VAS, ranging from 0 to 1, in which 1 represents perfect health. All the dimensions are grouped into three levels (no problem, some problem and extreme problem). We used a validated Chinese version[70] of the EQ-5D, which has been recommended by China Guidelines for Pharmacoeconomic Evaluations 2011 for a measure for HRQol and health utility.[71]

■ Anxiety and depression status

HADS will be used to identify and quantify two of the most common psychological disorders, anxiety and depression.[62] There is evidence of increased levels of anxiety and depression in people with LET.[72] HADS is a 14-item scale independent of somatic symptoms, which consists of two 7-item subscales measuring depression and anxiety, respectively. A 4-point scale (from 0 representing the absence of symptoms to 3 representing the maximum symptomatology) is used. The total scores for each subscale range from 0 to 21, with higher scores indicating higher levels of disorder. HADS has two cut-offs for categorization: 0-7, "non-case"; 8-10, "possible or doubtful case"; 11-21, "probable or definite case".[73]

■ Treatment success and recurrence rate

Participants' treatment impressions of change regarding their condition will be recorded on a 6-point Likert scale (from "completely recovered", "much improved", "somewhat improved", "same", "worse" to "much worse"). Success rates will be calculated by dichotomizing responses. Participants who report their overall condition as "completely recovered" or "much improved" since the beginning of the study will be counted as successes, while other responses will be counted as failures.[16,18] Recurrence will primarily be defined as occurring when a participant rates a success at 3 weeks and a failure at 2 or 6 months or one year on GROC.[16,18]

Additional treatments will also be recorded after the failure of management in this study (that is, not per protocol), if any, including subsequent interventions and even surgery.

■ Participants' satisfaction

Similarly, participants' level of satisfaction on the evolution of their condition will be determined on a validated 4-point Likert scale ranging from "very satisfied", "somewhat satisfied", "somewhat dissatisfied" to "very dissatisfied".[74]

2.9. Adverse events

All adverse events, defined as any negative or unwanted reactions to intervention, will be recorded through the symptoms reported by the patients, and observations by a researcher at every visit. US treatment may cause mild local swelling, spot-like bleeding, ecchymosis, enhanced local pain response, and local hyperesthesia or decrease. CI-related adverse events are divided into acute and long-term ones. Acute events include dizziness, skin flushing, local bleeding, and someone may even develop rarer physical reactions, such as arrhythmias. Therefore, all participants must take at least 20 minutes in the outpatient room to observe and even manage any acute adverse reactions following the injection. Long-term events may cause skin pigmentation, local calcification and infection.

2.10. Sample size calculation

Sample size and power calculation are based on the primary outcome of the PRTEE score. All sample size calculations assume two-sided analysis with a power of 90% (1-β=0.90) at a significant level of α=0.05. A standard deviation (SD) of 5.1-point on the PRTEE score will be used based on the previous trial.[75] To detect a minimum clinically significant difference of 11.0-point[56] (superiority margin) between US and control groups (assuming a true difference of 15.6-point[43,75]), a total of 22 participants

in each group is required. Allowing for an up to 10% dropout rate, we aim to enroll at least 24 participants in each group to complete the study.

2.11. Analysis plan

Baseline characteristics will be summarized for the three treatment groups using appropriate descriptive statistics. Both primary and secondary analysis will be conducted blind to treatment allocation and analyzed on intention-to-treat (ITT)[76] approach with all randomized participants retaining their original randomized group. Multiple imputation by chained equations will be used to address missing data caused by loss to follow-up and non-responses if these missing data are judged to be random.

The primary comparisons for PRTEE scores will be made using linear regression. In secondary analyses, repeated measures mixed model[77] will also be used to examine the associations between treatments and repeated outcome measures, with terms of treatment, time, trial center and corresponding baseline values as covariates (age, gender, body mass index, et al.). Linear regression will be used for numerical outcomes and logistic/ordinal regression for any categorical outcomes.

2.12. Quality assurance/monitoring/management

A Manual of Operations and Procedures (MOP) and case report form will be developed as per protocol to standardize all procedures and staff training in areas such as patient recruitment, outcome measurement, data entry, management, analysis, and security, which also include the monitoring plans to assure patient protection and data integrity, thus facilitating consistency in protocol implementation and data collection. The investigators, physicians, research assistants, outcome assessors and statisticians are different people and should receive Good Clinical Practice training. A trained project manager will visit each center for monitoring to ensure data quality and compliance with the trial protocol.

All data obtained will be kept strict and stored electronically on a database with secured and restricted access. Encryption will be used for data transfer, with removal for any information able to identify individuals. Data will be only de-identified for analysis at the completion of this study.

2.13. Study duration

Recruitment will begin in November 2021, and a one-year follow-up for all participants is anticipated to be completed by March 2023. See **Table 1** for time points and recruitment progress.

2.14. Ethics and dissemination

The study has been approved by all 4 Medical Ethics Committees, those are, Ethics Committee of Shanghai Sixth People's Hospital (the leading clinical center, approval No. 2021-153), Ethics Committee of Shanghai East Hospital (EC.D(BG).016.03.1-2021-096), Ethics Committee of Shanghai Tenth People's Hospital (SHSY-IEC-4.1/21-193/01), and Ethics Committee of Pudong New Area People's Hospital (IRBY2021-005). The potential risks of this clinical trial are considered to be minimal and are addressed in the protocol and consent forms. A written consent (**Supplementary 1**) will be obtained by clinical practitioners from each participant. The trial was registered on www.chictr.org website (registration number ChiCTR2100050547). Data will be published in peer-reviewed journals and presented at conferences, both nationally and internationally.

2.15. Limitation

This study will have one limitation. Participants and treating surgeons are inevitably not blinded, which may produce bias. However, we will strictly control the outcome assessors and statisticians to be blinded to group allocation and not involved in treatment procedures to reduce the bias.

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Figure Legends

Figure 1 Participant flow chart

Table 1 Study evaluation procedures and timeline

Study procedure	Medical evaluation	Enrolment visit	3 weeks	2 months	6 months	One year
Determine eligibility	√	√				
Obtain signed consent		√				
Obtain medical and demographic data		√				
Give instructions for pain medication diary		√				
Outcome measures						
Patient-Rated Tennis Elbow Evaluation		√	√	√	√	√
Visual Analogue Scale for pain		√	√	√	√	√
Shortened version of the Disabilities of the Arm, Shoulder and Hand questionnaire		√	√	√	√	√
Pain free/maximum grip strength		√	√	√	√	√
Work Limitations Questionnaire-25		√	√	√	√	√
EuroQol-5D		√	√	√	√	√
Hospital Anxiety and Depression Scale		√	√	√	√	√
Treatment success rate			√	√	√	√
Treatment recurrence rate				√	√	√
Participants' satisfaction			√	√	√	√

INDEX SECTION

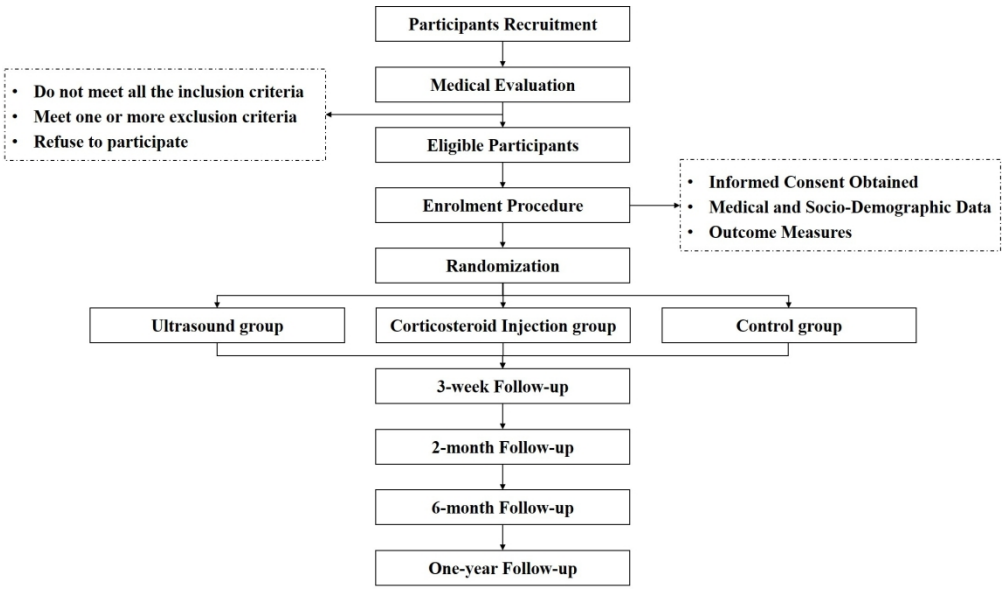

Figure 1/ Participant flow chart

365x212mm (150 x 150 DPI)

INFORMED CONSENT FORM

(English Version)

Participant Information Page

Study Title	:	Effectiveness of ultrasound therapy for the treatment of lateral elbow tendinopathy
Principal Investigator	:	Cunyi Fan
Sponsor	:	Shanghai Sixth People's Hospital

Dear participant:

You have been diagnosed with lateral elbow tendinopathy, and will be invited to participate in the study named "Effectiveness of ultrasound therapy for the treatment of lateral elbow tendinopathy". The study is conducted by the researchers themselves. Please read this informed consent carefully and make the decision whether to participate in this study or not. Participation in this study is entirely your choice. As a participant, you must give your written consent prior to joining the clinical study. When your doctor or researcher discusses informed consent with you, you can ask him or her to explain to you what you don't understand. We encourage you to discuss this thoroughly with your family and friends before making any decision to participate in this study. You have the right to refuse to participate in the study or withdraw from the study at any time without being penalized or losing your rights. If you are participating in another study, please inform your study doctor or investigator. The background, purpose, process and other important information of this study are as follows:

1. BACKGROUND

First described by Runge, lateral elbow tendinopathy (LET), also widely known as tennis elbow, has an estimated prevalence of 1% to 3% in the general population, and peaks at fourth and fifth decades of life, with an equal gender distribution. LET causes great burden on social economy, with an annual sickness absence rate as high as 5% in the working-aged adults. Though previously considered to be a "tendinitis", histological analysis suggests a degenerative rather than an inflammatory process in LET, which is now commonly converted to be considered as a "tendinosis". A LET diagnosis is usually straightforward, with clear clinical signs and symptoms. Patient most often complains of

pain at or around the bony surface of the upper half of the lateral epicondyle, and is likely to have a history of strenuous overuse relating to particular repetitive actions in the affected upper limb.

Though LET usually is a self-limiting condition, complaints may last up to 2 years or longer, therefore, it has great clinical value to find a better and faster recovery process. General principles of LET treatment should be orientated to pain relief, movement restoration, grip strength and endurance improvement, back to normal function and life quality, and control of further clinical deterioration. Treatments can be divided into operative and non-operative therapies. Invasive treatments commonly include open, arthroscopic and percutaneous release of the common extensor origin. Among these, Ultrasonic Percutaneous Tenotomy, a recent developed method, appealing to many researches for its good durability of pain relief and functional recovery, has a satisfied long-term (90 months) outcomes reported by Ang BFH. However, surgery is usually considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population; therefore, nonoperative treatment is suggested as first-line treatment. Generally, nonsurgical methods include injections (like corticosteroid, platelet-rich plasma, autologous blood, sodium hyaluronate, etc.), physiotherapy, extracorporeal shock-wave therapy (ESWT), ultrasound, topical glyceryl trinitrate, or oral naproxen, etc.

So far, despite the wide range of treatments; however, there is no successful and universally accepted regimen. In a cross-sectional survey of UK practice in managing LET, 81% experts recommended Exercise-based Therapy (EBT) as the first choice of intervention. EBT was also supported by high quality clinical trials and systematic reviews, regarding as the most cost-effective treatment for LET. The survey also showed that, as the mainstream treatment for a long time, corticosteroid injection (CI) was still the most recommended intervention second to EBT, due to its quick pain relief and physical functional improvement, though the recurrence rate may be high and prognosis may be worsened in the long term. In additional, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hyaluronate injection, platelet-rich plasma injection, ESWT and acupuncture still remain controversial or provide little to no benefit.

Ultrasound (US) is widely used for imaging purposes and regarded as an adjunct to physiotherapy. US can reduce muscle spasms and pain, and facilitate tissue repair by increasing local blood flow and stimulating inflammatory mediators. US has been widely reported to be treatment beneficial in fracture nonunions, osteoarthritis, chronic muscle pain, soft tissue injury, etc. As for tendinopathy, US is also reported to be a potential

noninvasive treatment modality for frozen shoulder, rotator cuff, achilles and patellar tendinopathy. Some studies have reported the efficacy of US in LET treatment, but with low grade of study design and data, and most of them focused on the comparison between US and ESWT. Both Yalvaç B and Özmen T have shown significant improvements in terms of pain, upper limb function, strength and life quality from baseline after treatment with US. However, they did not have a control group, which would make it unclear whether the efficacy come from US itself or passing time, as LET is a self-limited disease.

Therefore, the role of US in LET treatment still needs to be further explored by high-quality study. Additionally, to our best of knowledge, no study has compared the efficacy between US and CI in LET treatment yet.

2. STUDY PURPOSE

The purpose of the current three-arm, prospective, randomized, multicenter trial is to investigate the effectiveness of US in treatment for LET, that is, US versus CI versus control, with a fundamental intervention of EBT, on clinical and functional outcomes, including Patient-Rated Tennis Elbow Evaluation (PRTEE).

3. STUDY PROCESS

(1) How many people will participate in the study?

About 72 people will participate in the study at 4 municipal tertiary hospitals: Shanghai Sixth People's Hospital (leader unit), Shanghai East Hospital (participating unit), Shanghai Tenth People's Hospital (participating unit) and Pudong New Area People's Hospital of Shanghai (participating unit).

(2) What are the study procedures?

Before you are enrolled in the study, your medical history will be asked, and you will be screened for lateral elbow tendinopathy with a lateral elbow irritation test.

After determining that you are eligible to participate in the study based on inclusion and exclusion criteria, you will be collected and randomly assigned to treatment:

A. Characteristic features collection

You will be asked for your age, sex, body mass index, affected elbow, dominant arm, lifestyle (smoking and drinking), and previous medical history. As well as relevant questions about duration of symptoms and previous treatments (rehabilitation exercises, injections or others). Others like occupation, employment characteristics (full-time or part-

time work, manual or non-manual labor), employment status (whether on sickness absence), professional activity characteristics, and sports activities will be also collected.

B. Clinical features collection

You will complete the following questionnaires, including Patient-Rated Tennis Elbow Evaluation (PRTEE) for elbow function and symptom, Visual Analogue Scale (VAS) for pain, shortened version of the Disabilities of the Arm, Shoulder and Hand (Quick-DASH) for upper limb disability, pain free/maximum grip strength, Work Limitations Questionnaire-25 (WLQ-25) for functional limitations at work, EuroQol-5D (EQ-5D) for general health, Hospital Anxiety and Depression Scale (HADS) for mental status, Global Rating of Change for treatment success and recurrence rate, and Mahomed scale for participant's satisfaction.

C. Treatment by group

At the beginning, all of you will receive standardized education and advice on adjusting activity patterns and managing pain, which will be distributed in the form of printed brochures and orally assessed on their understanding of the content. You will be told that absolute rest of the arm will not be advocated, and activities that do not cause elbow pain should be encouraged. The primary physical impairment in LET, which occurs in the muscle system, is best characterized as a deconditioning response of the forearm muscles to the pain. Therefore, all of you will receive the internationally best recommended fundamental intervention, EBT program, for the forearm muscles. The EBT in this study will follow a standard protocol that has been adopted and used by several high-quality RCTs, mainly for addressing motor impairments, relieving pain and stimulating tendon remodeling. 30 minutes per day, including basic tasks (pain free [1] gripping and [2] extension exercise) and appendage tasks ([3] flexion, [4] supination and pronation, and [5] radial and ulnar deviation exercise). Various kinds of resistance and load can be used, like free weights, rubber bands, manual resistance, isokinetic dynamometry or isometric contractions. [6] It is essential that all exercises that are performed for the upper limb must be done with sound alignment of the spine, trunk and proximal arm.

You will be randomly assigned to one of three groups, [US group] vs. [CI group] vs. [Control group]:

(a) If you are assigned in the [US group], you will receive continuous mode US (Shanghai, China) at a frequency of 1 MHz and intensity of 1.0 W/cm^2 for 10 minutes in 5 days per week for 3 weeks on the maximum pain region of lateral elbow.

(b) If you are allocated to the [CI group], you will receive a single local infiltration of 1mL triamcinolone acetonide (10mg/ mL) and 1mL lidocaine 1%. Local corticosteroid injection was administered to the most painful area on pressure around the lateral

epicondyle. Participants will be advised to wait for 20 min following injection, and to inform their doctor if there is any suggestion of infection or other adverse events. All adverse reactions will be managed by a committee chaired by the chief investigator. Rest from all strenuous activity for 1-2 weeks following injection will be strongly recommended, followed by gradual return to normal activities. Participants will be instructed to avoid aggressive return to activities even if substantial relief is obtained, to minimize potential recurrence of their symptoms.

(c) If you are randomized to the [Control group], you will neither receive US therapy nor corticosteroid injection. They will only receive the fundamental intervention, EBT program.

We discourage additional treatments to that assigned (that is, not per protocol) during the intervention period, but we allowed the use of simple analgesics as needed. You will report all not per protocol treatments, such as drugs, in a diary.

D. Follow-up features collection

Follow-up data will be collected during your visits to the hospital at 3 weeks, 2 and 6 months, and one year after random assignment.

(3) How long will the study last?

This study will continue for 1 year from the time you receive treatment, and we will collect follow-up information from you at 3 weeks, 2 months, 6 months, and one year at your regular outpatient review.

You may drop out of the study at any time without losing any benefits to which you are entitled. However, if you decide to withdraw during the study, you are encouraged to talk to your doctor first. If you experience a serious adverse event, or if your study doctor feels it is not in your best interest to continue in the study, he or she may decide to withdraw you from the study. The sponsor or regulatory agency may also terminate during the study period. However, your withdrawal will not affect your normal medical treatment and rights.

If you withdraw from the study for any reason, you may be asked about your participation in the study. You may also be asked for a medical examination and follow-up questionnaire if your doctor deems it necessary.

(4) Information and biological specimens collected during the study

Biological specimens are not involved in this study, and the information collected is basic characteristics features, preoperative and follow-up clinical features (see the study procedures for details).

All data obtained will be kept strict and stored electronically on a database with

secured and restricted access. An encryption will be used for data transfer, with removal for any information able to identify individuals. Data will be only deidentified for analysis at the completion of this study.

4. RISKS AND BENEFITS

(1) What are the risks of participating in this study?

The risks you may incur by participating in this study are as follows. You should discuss these risks with your study doctor or, if you prefer, with your regular care provider.

US treatment may cause mild local swelling, spot-like bleeding, ecchymosis, enhanced local pain response, and local hyperesthesia or decrease. The occurrence of these reactions depends on the dose of treatment, the extent of the lesion, and the individual patient, and usually does not require special treatment. Severe adverse reactions can be treated locally, or prolong the interval of treatment, reduce the intensity of treatment. If the treatment does not improve or abnormal conditions occur, the treatment should be stopped and immediately go to the hospital.

CI-related adverse events are divided into acute and long-term ones. Acute events include dizziness, skin flushing, local bleeding, and someone may even develop rarer physical reactions, such as arrhythmias. The occurrence of these reactions depends on the individual patient, and usually does not require special treatment. In addition, during the injection, there may be a slight tingling sensation due to tissue and nerve damage in the skin. If the patient is physically sensitive, the pain may be more intense. Someone may even develop rarer physical reactions, such as arrhythmias. Therefore, all participants must take at least 20 minutes in the outpatient room to observe and even manage any acute adverse reactions following the injection. Long-term events may cause skin pigmentation, local calcification and infection. The drugs in the CI contain hormones, therefore, if are injected repeatedly and for a long time, it will cause damage to the tissues in the skin, so local calcification and skin stiffness occur. If the drug penetrates the bones, it can cause osteoporosis. After the injection, if the patient's physical condition decreases, and the wound is not kept clean, it may lead to bacterial invasion of the wound, so the wound healing speed will be slow, and there will develop infection and inflammation. These adverse reactions can be avoided by reducing the number of CIs and standardizing injection procedures.

EBT is exercise, and theoretically there are no complications.

If you experience any discomfort, new changes, or any unexpected conditions during the study period, whether or not related to the study, you should inform your doctor in a

timely manner, and he/she will judge and administer appropriate medical treatment.

During the study period, you need to visit the hospital on time and do some examinations, which will take up some of your time and may cause trouble or inconvenience to you.

(2) What are the benefits of participating in the study?

If you agree to participate in this study, you may receive direct medical benefits, such as accelerated relief of symptoms of LET. You can also have a deeper understanding of diseases and so on. In addition, we hope that the information gained from your participation in this study will benefit you or other patients with similar conditions in the future.

5. ALTERNATIVE TREATMENT OPTIONS

In addition to participating in this study, you may receive the other treatments provided by your doctor: corticosteroid injection, EBT, autologous blood or hyaluronate injection, platelet-rich plasma injection, ESWT, acupuncture, and surgery, etc.

Please discuss these and other possible options with your doctor.

Treatments can be divided into operative and non-operative therapies. Invasive treatments commonly include open, arthroscopic and percutaneous release of the common extensor origin. Among these, Ultrasonic Percutaneous Tenotomy, a recent developed method, appealing to many researches for its good durability of pain relief and functional recovery, has a satisfied long-term (90 months) outcomes reported by Ang BFH. However, surgery is usually considered for patients with persistent pain and disability after a course of well-performed conservative therapy, with a proportion as low as 3% in the whole LET population; therefore, nonoperative treatment is suggested as first-line treatment. Generally, nonsurgical methods include injections (like corticosteroid, platelet-rich plasma, autologous blood, sodium hyaluronate, etc.), physiotherapy, extracorporeal shock-wave therapy (ESWT), ultrasound, topical glyceryl trinitrate, or oral naproxen, etc.

So far, despite the wide range of treatments; however, there is no successful and universally accepted regimen. In a cross-sectional survey of UK practice in managing LET, 81% experts recommended Exercise-based Therapy (EBT) as the first choice of intervention. EBT was also supported by high quality clinical trials and systematic reviews, regarding as the most cost-effective treatment for LET. The survey also showed that, as the mainstream treatment for a long time, corticosteroid injection (CI) was still the most recommended intervention second to EBT, due to its quick pain relief and physical functional improvement, though the recurrence rate may be high and prognosis may be

worsened in the long term. In additional, systematic reviews have shown that the effects of other conservative treatments like autologous blood or hyaluronate injection, platelet-rich plasma injection, ESWT and acupuncture still remain controversial or provide little to no benefit.

6. USE OF RESEACH RESULTS AND CONFIDENTIALITY OF PERSONAL INFORMATION

Results conducted through this program may be published in medical journals with the understanding and assistance of you and other participants, but we will keep your study records confidential as required by law.

The personal information of study participants will be kept strictly confidential, and your personal information will not be disclosed unless required by relevant laws.

If necessary, government administrative departments, hospital ethics committees and other relevant researchers can access your data according to regulations.

7. RESEARCH EXPENSES AND RELATED COPENSATION

(1) Cost of drugs/instruments used in the study and related examinations

There are no potential additional costs for this study. Routine outpatient fees include registration, examination for LET, oral non-steroidal anti-inflammatory drugs, etc. There is no cost involved in EBT. The expenses related to US and CI injection will be borne by our research group and funding. In addition, you will be solely responsible for the expenses incurred by you for any treatment other than this study, as well as for the routine treatment and examination required for any concurrent disease.

(2) Compensation for participation in the study

There are no additional compensation costs for this study.

(3) Compensation/compensation after damage

For participants who suffer damage related to this study, the sponsor Shanghai Sixth People's Hospital will bear the treatment cost and corresponding economic compensation in accordance with Chinese laws and regulations.

8. RIGHTS OF PARTICIPANTS AND RELEVANT MATTERS NEEDING

ATTENTION

(1) Your rights

Your participation in the study is voluntary throughout the entire process.

If you decide not to participate in this study, it will not affect other treatments you should receive.

If you decide to participate, you will be asked to sign this written informed consent. You have the right to withdraw from the trial at any stage without discrimination or unfair treatment, and your medical treatment and rights will not be affected.

(2) Matters needing attention

As a subject, you are required to provide true information about your medical history and current medical condition;

Inform the study doctor of any discomfort observed during the study;

Do not take any restricted drugs, food, etc. as advised by your doctor;

Tell the study doctor if you have recently participated in or are currently participating in other studies.

During the intervention, we discouraged additional therapy (i.e., not according to the grouping protocol), but we permitted the use of analgesics when needed (only acetaminophen and NSAIDs).

For medications taken, the name, dose, frequency and duration will be recorded at all follow-up visits.

9. RELEVANT CONTACT INFORMATION

If there is any significant new information during the study that may affect your willingness to continue to participate, your doctor will inform you promptly. If you are interested in your own study data, or you would like to know the findings after this study, you may ask any questions about this study at any time and receive answers accordingly, Please contact doctor Ziyang Sun at **********.

Participant Signature Page

Informed Consent Statement:

I have been informed of the purpose, background, process, risks and benefits of this study. I have plenty of time and opportunity to ask questions, and I am satisfied with the answers.

I am also told who to contact when I have questions, want to report difficulties, concerns, suggestions for research, or want further information, or to help with research.

I have read this informed consent and agree to participate in this study.

I understand that I may choose not to participate in the study or withdraw from the study at any time during the study without any reason.

I already know that if I get worse, or if I have a serious adverse event, or if my study doctor decides it's not in my best interest to continue, he or she will decide to withdraw me from the study. The funder or regulatory agency may terminate during the study without my consent. If this happens, the doctor will inform me and the study doctor will discuss other options with me.

I will be provided with a copy of the informed consent which contains my signature and that of the investigator.

Participant Signature: _____

Date: _____

(NOTE: If participant has no capacity/limited capacity, legal representative signature and date will be required)

Legal Representative's Signature: _____

Date: _____

Investigator Signature: _____

Date: _____

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	4/6

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4/6
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	3
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	2
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2/3
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	2/3

Introduction

Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-10
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	8-10
Objectives	#7	Specific objectives or hypotheses	10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	10
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	11-12

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	13-15
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	13-15
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13-15
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-15
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	16-20
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	22

Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20-21
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-16, 21-22
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15-16, 21-22
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values).	15-16, 21-22

		Reference to where details of data management procedures can be found, if not in the protocol	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	21
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15-16, 21-22
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15-16, 21-22
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial	20

		conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	22
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	22
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	22
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22
Declaration of	#28	Financial and other competing interests for principal	22

interests		investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20-22
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	21-22
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21-22
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21-22
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21-22
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	22
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	/