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.

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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: _____