PROTOCOL

Full Study Title : A Prospective, Controlled, Randomised, Double Blind, Single Centre Study, Comparing the Effectiveness of Physiotherapy and Image Guided Injection of the Lateral Epicondyle of the Common Extensor Tendon with either Sodium Hyaluronate with Mannitol (Ostenil Tendon™), Platelet Rich Plasma (PRP), or Sham Injection on Pain and Function in Patients with Lateral Epicondyle Tendinosis.

Modified title compliant with character restrictions on clinicaltrials.gov register:

A Prospective, Double Blind, Single Centre, RCT, Comparing the Effectiveness of Physiotherapy in addition to one of 3 types of Image Guided Injection of the Common Extensor Tendon, on Pain and Function in Patients with Tennis Elbow.

Version 10

23rd May 2018

Brief Title: Comparing Injection Treatments for Tennis Elbow (CITTE) Trial.

IRAS number 223134

Investigators: Professor Adam Watts

Study venue: Wrightington Hospital

Aim : To determine the effect of a structure physiotherapy programme and a single image guided peri-tendinous injection to the lateral epicondyle, of either; Sodium Hyaluronate with mannitol (Ostenil Tendon™), Platelet Rich Plasma (PRP), or sham Injection on pain and function in patients with established elbow tendinopathy.

Background.

Tendinopathy of the common extensor tendon is one of the most prevalent musculoskeletal disorders of the arm, typically attributed to excessive use of the extensor and/or flexor muscles of the wrist, it is an overloading-induced injury resulting in pain and functional disability, often leading to limitation or cessation of activity and absence from work. Historically this syndrome has been referred to as lateral epicondylitis, which presents somewhat of a misnomer as histological evaluation typically displays no evidence of either acute or chronic inflammation.[1,2] Rather, repetitive muscle contraction leads to a neurocellular response provoking degradation by enzymes leading to angiofibroblastic degeneration and collagen disarray. Thus the current nomenclature includes 'lateral epicondyle tendinopathy', 'lateral epicondyle tendinosis', 'lateral epicondylalgia' or, more colloquially, 'tennis elbow'.[2]

Prevalence amongst the general population is reported to be between 1 and 3 percent, with an incidence rate of general practice consultations estimated to be between 0.3 to 1.1 per 100 population per year.[1,3,5] Peak prevalence has been documented to be highest amongst subjects aged 45–54 years.[5] No distinct correlation has been identified between gender and incidence, however the condition appears to be more persistent and of greater symptomatic severity in females.[6] Smoking and obesity have been identified as associated risk factors.[5] Typical episodic duration lasts, on average, 6 to 24 months.[7] The dominant arm is affected in 75% of cases, reinforcing the view of the condition as an overuse syndrome.[8] Despite the sporting connotation, tennis players represent only 5% of all lateral epicondyle tendinopathy cases seen in clinical practice; yet between 40 to 50% of racket sport players will be diagnosed with the condition in their lifetime.[9,10] Most presentations are idiopathic in nature, not necessarily induced by sport, but associated with physical load factors: repetitive, manually intensive, high force demands.[4]

ANATOMY AND DIAGNOSIS.

The lateral epicondyle of the humerus provides attachment to the origin of the extensor carpi radialis brevis (ECRB), the extensor carpi radialis longus (ECRL), the extensor digitorum and the extensor carpi ulnaris - the primary motion of this muscle group is to extend the hand at the wrist. The primary locus of pathology in tendinopathy of the ECRB tendon is at the origin on the lateral epicondyle. Tendons are considered to be predisposed to degeneration at their insertion points, due to their relative hypovascularity in this region[3]

Diagnosis of lateral epicondyle tendinopathy, which has a well-defined clinical presentation, is based on patient symptoms, a thorough consideration of the patient's history, and physical evaluation. Imaging modalities are not required for diagnosis, although these can serve to more

fully determine the extent of tissue damage and identify differential diagnoses. Onset of lateral epicondyle tendinopathy commonly occurs with an absence of traumatic injury but rather as a gradual onset of symptoms.[4] Upon clinical examination, the area of maximum tenderness is usually defined distal to the origin of the extensor muscles of the forearm at the lateral epicondyle. Pain is exacerbated by active and resisted movement of the forearm. Range of motion may be affected in severe cases especially first thing in the morning and swelling may be observed in individuals with less subcutaneous fat.

Treatment Options

There are various treatment options available for lateral epicondyle tendinopathy. At present, however, there is a lack of objective evidence to support a universal consensus as to which constitutes the most effective or "Gold Standard" therapeutic intervention. Whilst no formal guidelines exist, a conservative approach has been advocated for initial management, with over 90% of lateral epicondyle tendinopathy cases successfully resolving within 2 years of non-surgical treatment, although surgery remains the ultimate option for those who fail to respond sufficiently to non-operative measures.[2,11]

Over 80% of patients with lateral epicondyle tendinopathy report improvement within 1 year, which supports the often adopted wait-and-see policy.[7] Within this period, workload and activity modification is recommended to remove any exacerbating stimulus, relieve strain and allow time for healing.[12] Topical non-steroidal anti-inflammatory drugs (NSAIDs) may provide beneficial relief from pain compared with placebo in the short term (3-4 weeks)[13-16]. Oral NSAIDs have not been found to provide longer-term effects (> 4 weeks), however the risk of gastro-intestinal adverse effects is significantly increased.[13-17] The Cochrane review of NSAIDs for treating lateral elbow pain concludes that evidence on which to base recommendations for the longer-term use of NSAIDs is insufficient.[14] Local corticosteroid injections have been found to provide beneficial short-term therapeutic effect (< 6 weeks), however this was not continued into the intermediate (6 weeks to 6 months) or longer (> 6 months) terms.[15,18-19] Biset *et al.* found corticosteroid injection to be superior compared with physiotherapy at 6 weeks, however high reoccurrence rates were observed (47 of 65 patients deemed initial successes subsequently represented), and long term outcomes were found to be significantly poorer compared with physiotherapy.[20] Adverse effects include: post-injection pain, skin depigmentation, subcutaneous fat atrophy, and, in some instances, tendon and ligament rupture.[21,22]

HYALURONIC ACID

Hyaluronic acid (HA) is a naturally occurring polymer, ubiquitous to the human body. HA, in its aggregated form, is an important structural component of the articular cartilage matrix, imbibing water molecules to provide cartilage resilience to compressive forces. Unaggregated, HA is the main macro-molecular constituent of synovial fluid and is fundamental to its characteristic viscoelastic properties. This enables the intra-articular fluid to function as a lubricant and a shock absorber between congruent cartilaginous surfaces. HA does not only

exert a positive mechanical effect but serves a biological role, regulating matrix turnover and joint homeostasis, promoting the release of prostaglandins and interacting with various inflammatory mediators, inhibiting phagocytic activity of macrophage and leukocytes, and thus conferring a chondroprotective effect. [23-25] Viscosupplementation with HA is well established internationally as a safe and effective intervention in the management of osteoarthritis.[26-29] Furthermore, administration of exogenous HA has been shown to offer significant therapeutic benefit within degenerate or compromised peri-articular structures, such as rotator cuff disease and lateral ankle sprain.[30-31] HA is secreted by the tendon sheath and, as for joints, allows for smooth tendon gliding and contributes to the nutrition of the tendon. Peri-tendinous and intra-sheath instillation of HA for the treatment of tendon disorders is generating a rapidly growing research base, with promising clinical results and few reported adverse events to date.

The natural tendon healing process proceeds along a complex pathway beginning with inflammation and cellular proliferation, followed by tissue formation and maturation, with each phase lasting days, weeks, and months, respectively. Following tendon damage, a common and inevitable complication is the formation of peri-tendinous adhesions; these fibrous agglutinations form between the tendon surface and overlying tissues, inhibiting tendon gliding and impeding tendon repair.[32] The basic premise of intra-sheath or peri-tendinous HA injection is to promote both tendon gliding and the tendon repair process - HA is naturally antagonistic towards fibronectin, the pre-cursor to cell-cell adhesions, and plays a crucial role in proliferation and differentiation of various cells.[33] Comper et al. found that HA forms a macromolecular network which functions as a barrier to the diffusion of fibronectin, thereby reducing the formation of a fibrin web, which in turn suppresses adhesion formation.[34] Yoneda et al. found concentrations of more than 1 mg/mL HA inhibit fibroblast proliferation, thereby reducing the amount of adhesions.[35] As to the ability of HA to suppress adhesion formation yet not impede the healing process, Bentley et al. reported that the natural response in surrounding tissue following trauma is an increase in the concentration of hyaluronic acid.[36] Hellstrom et al. conclude that HA may help tendon healing process by affecting the orientation of fibroblasts and collagen fibres and thus accelerate the reorganisation process of fibrous layers, reducing scar formation and tissue granulation.[37]

Hart et al. conducted a meta-analysis of 41 studies to determine the efficacy and risk of adverse effects of peritendinous corticosteroid and other injection therapies in the management of tendinopathy.[38] Hart concluded that corticosteroid injection is beneficial in the short term for the treatment of tendinopathies but may be worse than other treatments in the intermediate and long terms, and that no clear evidence of benefit of other injections was shown, except for HA in the short and long terms. Saito et al. conducted a meta - analysis into therapeutic effects of subacromial HA injection in patients with chronic shoulder pain.[39] 19 randomised controlled trails were included totalling 2,120 patients. The study concluded that HA injection is effective for the relief of pain and is a safe alternative to corticosteroid injection for chronic painful shoulder. Ostenil™ (HA) has been shown to substantiate these findings in patients presenting with primary subacromial impingement syndrome, with Funk *et* al concluding "HA appears to be as effective as depomedrone in reducing subacromial impingement pain but does not produce the pain surge associated with depomedrone in the first 72 hours post-injection."[40]

Petrella *et al.* evaluated the treatment of 331 competitive racket sport athletes with chronic lateral epicondyle tendinopathy (> 3 months) in a double-blind, randomised, placebo-controlled trail over a one year period.[41] 2 subcutaneous injections were administered, of either1% Sodium Hyaluronate (SH) or saline injection: the first injection at baseline evaluation, the second one week later. Post-injection care of rest, ice, compression, and elevation was instructed and no formal adjunct physiotherapy was prescribed. VAS pain at rest significantly improved in the HA group compared with control, which corresponded to a statistically significant improvement in maximal grip strength. These differences persisted at the 90-day and 365-day follow-up appointments. Time to return to pain-free and disability-free sport was 18 days in the HA group, but was not achieved at any time point within the study in the control group.

Ostenil Tendon™, a novel, patented 2% concentration of fermentative source HA with the addition of Mannitol has previously been shown to relieve pain and improve function in patients with partial thickness tears of the supraspinatus tendon and in patients with Achilles, lateral epicondyle and peroneal tendinopathies.[42, 43]

PLATELET-RICH PLASMA

Platelet-rich plasma (PRP) describes an autologous blood plasma fraction, enriched with platelets, thus presenting a high concentration of protein growth factors. The extracted and prepared fluid is injected at the sight of tendon injury, theoretically acting as an adjuvant to complement and promote the natural healing process. The use of PRP in the management of musculoskeletal injuries has increased, based on in vitro studies reporting an enhancement of the recruitment, proliferation, and differentiation of the cells involved in muscular tissue regeneration.[44]

PRP exerts it effects via the degranulation of the α-granules in platelets, which release various fundamental growth factors and cytokines; active secretion is initiated by the blood clotting process and begins within 10 minutes of clotting.[45] As the platelets are activated, the growth factors are secreted from the cell through the cell membrane, the secreted growth factors immediately bind to the external surface of cell membranes within the wound, and in turn induce an activation of an endogenous internal signal protein, which causes the expression of a specific gene sequence of the cell such as cellular proliferation, matrix formation, osteoid production, or collagen synthesis.[44]

Mishra *et al*. evaluated 140 patients with lateral elbow tendinopathy; patients had initially undergone a standardised physical therapy protocol and a variety of nonsurgical treatments. 20 patients experienced persistent pain and failed to respond adequately, this cohort were then given either a single percutaneous injection of platelet-rich plasma or bupivacaine as a control.[48] Eight weeks post-injection, the study group reported a 60% improvement in pain

compared with a 16% improvement in the control group. At six months response within study group had increased to 80% improvement.

De Vos *et al*. recently published a systematic review of PRP injections for chronic lateral epicondyle tendinopathy.[46] Five of the six studies included found no significant benefit in the study group compared with their respective controls at follow-up. The final study showed a beneficial effect compared with corticosteroid injection.

Krogh *et al*. examined whether a single injection of platelet-rich plasma (PRP) is more effective than saline or glucocorticoid in reducing pain in adults with lateral epicondyle tendinopathy at three months post-injection.[47] The authors conclude that neither injection of PRP nor glucocorticoid was superior to saline with regard to pain reduction in lateral epicondyle tendinopathy at the primary end point (3 months), however the study may be criticized due to the needling technique used to administer the saline, as this may have a therapeutic effect.

The current study will seek to identify any statistically significant differences in pain and function, as evinced by validated objective and subjective measures, in patients with a diagnosis of Lateral Epicondyle Tendinopathy/Entheseopathy, following a single, peri-tendinous injection into the affected elbow, administered under real time ultra-sonographic imaging, of either; 2ml 2% solution of Non-Animal Derived, Non-Chemically Modified Sodium Hyaluronate with Mannitol (Ostenil Tendon), or 2ml of PRP prepared with the Biomet Recover Miniplatelet System, reported to provide 8x the circulating concentration of platelets, or a subcutaneous sham injection under ultrasound control. All patients will undergo a standardised physiotherapy programme post injection.

Methodology.

Study Design. Prospective, randomised, controlled, double blinded, single centre trial.

Selection Criteria. Invitations to participate in the study will be extended to male and female patients, 18 years and above, referred to the Orthopaedic Departments who receive a diagnosis of Lateral Condyle Tendinosis (with or without degenerative changes) with symptoms present for > 3 months, whose symptoms and clinical evaluation warrant the prescription of a peri-tendinous injection to relieve symptoms and who are competent to give informed consent.

Demographic data collection
Age
Handedness
Occupation
Ethnicity

Exclusion Criteria.

- Absence of tenderness at the lateral epicondyle.
- Congenital or traumatic bio-mechanical deformities of Elbow complex.
- Previous Corticosteroidal, Local Anaesthetic, PRP or Hyaluronic Acid injections to target elbow within the last three months.
- Known hypersensitivity to PRP, Hyaluronic acid or any excipients associated with any of the prescribed injections.
- Known contra-indication to any treatments constituting normal/appropriate therapy in the view of the Consulting clinician.
- Ipsilateral arm pathology severe enough to cause confusion of localised pain perception.
- Pregnancy, lactating women, local infection.
- Pain score less than 4/10
- Patients commenced on medication for the treatment of anxiety or depression within the last 6 weeks
- Previous involved in research in last 12 months
- Any progressive, degenerative neuromuscular disorder

Withdrawal Criteria.

Patients may be withdrawn from the study when:

- Patient expresses desire to withdraw.
- Major repeated protocol deviation
- Non-compliance of patient

Adverse event and Side Effect Reporting.

Any adverse event reported by a participating patient to a member of the clinical care team at any follow up visit, or between visits to the patient's GP or other physician will be recorded and detailed in an AE report. The lead investigator will examine the reporting patient as soon as possible following the generation of a report and where appropriate, order any tests or prescribe such medicines or treatment as deemed to be necessary.

If any patient is admitted via Accident & Emergency for any reason either connected or unconnected with the study, either the lead investigator or a designated member of the clinical care team will liaise with the appropriate Consulting clinician. The details of any reported AE will be specified in terms of subjectively reported symptoms and sensations, along with a qualified medical opinion from either the lead investigator or a designated member of the clinical care team as to likely cause of any signs or symptoms presenting at examination. Where diagnostic tests (e.g. blood tests, laboratory cultures) are ordered, a copy of the test results will be appended to the patient record card. Following due scrutiny, any side effects in either study group will be determined as either; 1. Unrelated to study treatment in any way. 2. Related to injection (needle placement, injection site reaction to needling, infection). 3. Related to local anaesthetic, as designated on the summary of product characteristics under known side effects. 4. Related to PRP, as designated on the summary of product characteristics under known side effects. 5. Related to Ostenil Tendon™, as designated on the summary of product characteristics under known side effects.

Procedure.

Recruitment: In order to encourage timely recruitment for this study, local GPs will be informed by letter that the study is ongoing and will be sent a copy of the study protocol for their information. This will allow GPs to discuss the study with any potentially eligible participants presenting to them with Tennis Elbow, to establish if the participant wishes to be referred to the host Trust to be offered the opportunity to participate in the study. The GPs will not themselves be recruiting patients to the study, and it will be made clear to any patient expressing an interest in participation, that their eligibility for inclusion will be decided by their treating consultant as described below.

At their initial outpatient appointment, potential participants will be thoroughly examined by their treating consultant or a senior member of the consultant's team. A clinical diagnosis will be confirmed by careful history-taking and examination, and only those patients with a diagnosis of lateral epicondylosis, who meet the inclusion criteria, will be informed about the study. These individuals will receive a brief verbal explanation of the study by their treating clinician and they will also be provided with a copy of the study participant information sheet to read at their leisure. Alternatively, any patients eligible for recruitment in this study who had already been listed for a PRP injection prior to the start of this study, will be contacted by post via the treating consultant's team, with a copy of the PIS and a covering letter. The letter will explain that their consultant has identified that they may be eligible for inclusion in the study

and they are invited to read the PIS and consider the option of participation. The letter will also explain that unless they contact the consultant's secretary to object, a member of the research team will contact them by telephone to establish if they are interested in taking part or if they have any questions regarding the content of the PIS. Should they wish to discuss the study further with a member of the research team in person, a convenient time for them to attend the hospital to do so will be arranged.

When the patient attends the hospital for their pre-operative assessment, they will then be approached by a member of the host Trust research team who will answer any further questions they may have about the study procedures and record their informed consent if they decide to proceed with participation.

Consenting participants will be randomised to Study Group A (physio and PRP), Study Group B (physio and Ostenil Tendon™), or Control Group C (physio and sham injection) once informed consent has been recorded and baseline data has been collected.

Treatment and follow-up will be the same for those patients who wish to take part in the study and for those patients who decline to take part but whose condition makes a peri-tendinous injection clinically appropriate. Following informed consent, patients will be assessed for demographic detail (age, gender, ethnicity, occupation, affected elbow, height and weight/BMI, duration of symptoms, relevant diagnosis, current medication), and given patient completed questionnaires to assess pain and function (Oxford Elbow Score (OES), Quick DASH Score, 100 mm visual analogue pain scale with terminal descriptors), Hospital Anxiety and Depression (HAD) Score and asked to complete EQ5D at the initial consultation (V1).

Treatment: Consenting patients will attend for the injection to be administered under ultrasound guidance. All participants will have 30ml of whole venous blood withdrawn under aseptic conditions.

Out of sight of the patient the whole venous blood will either be;

placed in the cell separator and centrifuged at 32000 rpm for 15 minutes for subjects in group A. During the centrifugation process 2ml of 2% plain lidocaine will be injected into the subcutaneous layer at the site of injection of the PRP. One millilitre (2ml) of PRP produced will be drawn into a syringe wrapped in silver foil and injected under ultrasound control via a blue (20 gauge) hypodermic needle into the lateral epicondyle using a peppering technique.

Or

discarded for those in group B and C. The centrifuge will be set to run at 32000rpm for 15 minutes with a saline counterbalance. During the centrifugation process 2ml of 2% plain lidocaine will be injected into the subcutaneous layer at the site of injection. For those in group B a pre-prepared "Ostenil Tendon" syringe will be wrapped in silver foil and 2ml will be injected into the peri-tendinous area via a blue (20 gauge) hypodermic needle under ultrasound control.

For those in group C an empty syringe wrapped in silver foil with a blue (20 gauge) hypodermic needle will be used to perform a sham injection into the subcutaneous tissue only by passing the needle into the tissue with no injectate.

During the procedure the patient will be distracted by being asked to confirm their personal details.

Patients will be given pain report diaries which will be completed on days 1, 2, 3, 7, and 14, and at 6 weeks, 12 weeks (final clinical follow up visit prior to discharge). Patients will be taught home exercises by a blinded physiotherapist prior to discharge, a formal class based physiotherapy programme will commence at 5-15 days post injection. The patient will be assessed by a blinded clinician at 3 months and 12 months post treatment. Telephone follow-up calls will be made to patients 3 months and 12 months post treatment if the patient declines to attend a follow-up appointment. The Consulting physician will discharge patients from his direct care at 12 weeks unless enduring or subsequently manifesting symptoms persist. Pain scores, amount of rescue medication (codeine & Paracetamol) and QOL questionnaires will be completed at all visits. The OES, qDASH, HAD and EQ5D will be completed at 3 and 12 month reviews.

Patients who successfully complete both 3 month and 12 months outcome questionnaires with be entered into a raffle to win an iPad tablet computer.

Primary Measure of Outcome.

The difference in Objective Functional Assessment as evinced by Quick DASH, at 12 months

Secondary Measures of Outcome.

The difference in Objective Pain and Functional Assessment as evinced by OES and 100 point VAS with terminal descriptors at 12 months

Change in EQ5D General Health Questionnaire.

Relationship of pre-injection HAD score to outcome.

Change in HAD score at 12months

Use of Rescue Medication.

Number of Patients.

The proposed randomized controlled double blind (single centre) trial design will have 80% power (1-β) to reject the null hypothesis, with an α (type I error, i.e. level of statistical significance) set at 0.05. Assuming a clinically significant [mean] difference (δ) of 15 Q-DASH score units between groups together with an estimated sample standard deviation (σ) of 22.5 (Biomet study – based on Q-DASH score for PRP arm) which gives an 'n' for each trial arm (assuming equal group sizes) of at least 35 analyzable patients in each of the three groups (A,B &C) and given a possible attrition rate of about 16% the CITTE trial will probably therefore need a total sample size of at least 123 of patients, approximately.

Statistical Analysis.

All quantitative data - age, gender, duration of symptoms, disease progression, target joint, Height, weight and BMI, will be analysed using the most appropriate non-parametric tests. VAS, qDASH and OES score Inventories, EQ5D, Blinded Assessor and escape medication scores will be tested for homogeneity of variance (Chi sq/F test), mean scores calculated, and then either *t* tested (with possible ANOVA for correlations between pain, function, strength etc) or Mann-Whitney/ Wilcoxon rank sum (Kruskall Wallis differences /Jonkheere trend).

Interventions

Physiotherapy protocol

After the injection and prior to discharge a physiotherapist will teach patients eccentric loading exercises of the wrist extensors. They will be instructed to commence the exercises at day 1 post injection. They will be advised to carry out 3 sets of 15 repetitions, 3 times per day. An accompanying exercise sheet will advise to increase the load as symptoms permit. It will be suggested to commence with a half filled 500ml bottle of water. In addition a simple common extensor stretch will be taught to use following the eccentric exercises.

At 5-15 days post injection the patients will commence an out-patient class based physiotherapy programme. The class will be held 2 weekly by a blinded physiotherapist. After being taught the exercises on an 1:1 basis, the patients will be supervised during a circuit style exercise programme. The exercise programme will include eccentric loading of the common extensors, and upper limb strengthening involving the full kinetic chain, in particular the rotator cuff and scapular muscles. Each patient will be supervised and monitored to improve technique, and to increase the load. Patients will be provided with a home exercise programme which will reflect the class exercises.

Study GROUP A Product Dose, Presentation, and Mode of Administration.

2ml unbuffered PRP prepared with **Zimmer/Biomet Recover Mini-platelet** system administered via intratendinous injection under ultrasound.

Study GROUP B Product Dose, Presentation, and Mode of Administration.

Ostenil™ Tendon (40mg/2ml of bio-fermentation source Sodium Hyaluronate with 10mg Mannitol in a pre-filled syringe). To be administered via peritendinous injection under ultrasound.

Licensed indication in the EU: **For the treatment of pain and restricted mobility in tendon disorders.**

Active Ingredient; Sodium Hyaluronate / Mannitol

Excipients Sodium Chloride, Sodium Monohydrogenphosphate, Sodium Dihydrogenphosphate, water for injection.

Distributor: TRB CHEMEDICA (UK) LTD
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Study Group C Product Dose, Presentation, and Mode of Administration.
A sham injection under ultrasound control. No fluid will be instilled.

Pain Relief Controls

All patients will be asked not to take NSAID for a week before and two weeks after injection. Paracetamol 1g QDS and codeine phosphate up to 30mg QDS will be permitted.

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