“Clinical comparative effectiveness of acupuncture versus manual therapy treatment of lateral epicondylitis”

A pilot for a randomized controlled trial

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Trykk: Reprosentralen, Universitetet i Oslo
Abstract

**Background:** Lateral epicondylitis (LE) or tennis elbow is the most common chronic musculoskeletal pain condition affecting the elbow. Given the complexity of the pathophysiology of LE, we propose a multimodal approach for the management of this condition. Manual therapy (elbow mobilization) in addition to eccentric exercise has a superior benefit over wait and sees. Acupuncture compared with sham treatment is effective in short-term relief of pain in LE, but there is little knowledge on the comparative effectiveness of manual therapy and acupuncture treatment of LE, in means of pain relief.

**Objective:** The objective of the present study was to investigate the clinical effectiveness of acupuncture and manual therapy treatment of LE, in an institute of sports medicine and rehabilitation. Both treatments were in addition to eccentric exercise, and were compared with eccentric exercise alone, assessed during a 12-week follow-up.

**Methods:** A pilot for a randomized controlled trial was conducted in the city of Oslo, Norway. We included 36 women and men with clinically diagnosed LE, and randomly assigned the patients to one of three treatments: eccentric exercise alone, acupuncture in addition to eccentric exercise or manual therapy in addition to eccentric exercise.

**Results:** The result of the analyses was significant for differences in mean score pain relief for treatment groups compared to exercise alone, all measurements considered. Further, the acupuncture group was highly significantly different from the exercise alone group (p<0.001). However, this difference in estimated mean scores, reached only borderline significance when compared with the manual therapy (all measurements considered). Patients in exercise alone had significantly higher mean pain score than treatment groups, the estimated mean pain score for exercise alone (all measurements considered) with 95 % CI was 4.04 [3.56; 4.51], and 2.82 [2.46; 3.18] for acupuncture and 3.37 [2.88; 3.86] for manual therapy group.

**Conclusion:** Patients receiving treatment in addition to eccentric exercise, either acupuncture or manual therapy experienced a better pain relief than those receiving eccentric exercise alone, during treatment and up-to 12-week follow-up. In addition, in explorative analysis a gender difference emerged; females had higher levels of pain than males, more dominantly, in-group of exercise alone. Explorative analysis showed some differences in pain relief.
between acupuncture and manual therapy, but the differences were of debatable clinical value.

This pilot study indicate that the methods and procedures are feasible, and the results of the pilot is worth following up in a subsequent larger study.

**Keywords:** Lateral epicondylitis, tennis elbow, eccentric exercise, acupuncture, physiotherapy and manual therapy
Acknowledgements

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Oslo, november 2016

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Abbreviations

CONSORT: Consolidated standards of reporting trials
CGRP: Calcitonin gene related peptide
DASH: Disabilities of the arm shoulder and hand
LE: Lateral epicondylitis
MWM: Mulligan’s mobilization-with-movement
MIC: Minimal important change
MRI: Magnetic resonance imaging
NIMI: Norwegian Institute of Sports Medicine
NRS: Numeric rating scale
NSD: The Norwegian Centre for research Data
PROMs: Patient reported outcome measures
RCT: Randomized Control trial
REK: Regionale komiteer for medisinsk og helsefaglig forskningsetikk
ROM: Range of motion
SD: Standard deviation
US: Ultrasound
1 Introduction

My work as a physiotherapist during the past 18 years has focused on pain management and rehabilitation of musculoskeletal conditions. The encounter with those patients has inspired me to explore and learn new skills, like acupuncture. Clinical practice has been a constant motivation for me to seek new knowledge. Hence, applied to the Master’s Degree Program at Department of Health Sciences, Faculty of Medicine at University in Oslo.

The article is the heart of this thesis, and my recommendation is to read it first. It is the finished product of the present study; a pilot of a randomized controlled trial (RCT). Exploring the effectiveness of different treatment modalities of tennis elbow in a clinical setting. We titled it; “Clinical comparative effectiveness of acupuncture versus manual therapy treatment of lateral epicondylitis”

1.1 Background

Lateral epicondylitis (LE), or more commonly known as tennis elbow, is a common soft tissue condition, treated by many physical therapists in a variety of clinical settings. LE is causing significant pain and functional disability from work, sports and leisure activities. Furthermore, also high costs due to productivity loss and health care use. Several work-related physical and psychosocial factors have been associated with an increased occurrence of LE. Despite decades of research, investigating treatments and the underlying mechanisms of LE, it remains a challenging condition for therapists and researchers alike.

1.1.1 The epidemiology of LE

Approximately 40 % of people will experience LE at some point in their life. The annual incidence is four to seven cases per 1000 patients in general practice, and as high as 17 % of workers in highly repetitive hand task industries. The disease onset is most common between 35 and 54 years of age, with an average first appearance at 42 years. Some studies indicate that men and women are equally affected; others report a higher percentage of affected women.
1.1.2 The socioeconomic burden of LE

LE most commonly affects the dominant arm, particularly when performing repetitive activity, so it is not surprising that the greatest burden of LE is among manual working populations\(^6\). In occupations with manual work injuries in musculoskeletal upper limb, are the reasons for some of the longest work absences. LE is associated with prolonged sickness absence in 5% of affected working-aged adults\(^2\). Neck pain, concurrent rotator cuff pathology and office work are also significant associated with LE\(^1\). Research supports that it is a possible connection between intensive use of computers and incidents of LE\(^7\).

Dr. James Cyriax suggested in 1936 that the natural history of LE is between 6 months and two years, and he has been widely cited since\(^8\). Recent studies have shown that symptoms in LE may persist for more than two years and recurrence is common. Further, those with high baseline severity of pain and disability of elbow are much more likely to have symptoms after 12 months, regardless of treatment\(^5-6\). Other factors, which predict a poorer prognosis, are co-morbidities like neck pain and shoulder disorders\(^1\). Therefore, LE is not self-limiting and is associated with ongoing pain and disability.

1.2 Etiology of LE

The first description of LE is back in 1883, originally called lawn tennis elbow\(^8\). Over the years, the term tennis elbow has been used to describe a variety of maladies that relates to this region of the elbow. To eliminate confusion, it is important to define the term accurately. For some time, it was suggested that LE involved an inflammatory process, hence the name. Consistent absence of inflammatory cells has resulted in the consensus that the process is non-inflammatory in nature, and reconsidered as degenerative\(^8-9\). Today, there is an understanding that LE, or tennis elbow is failed tendon healing, as in tendinopathy\(^5-6\).

1.2.1 Management of LE

Since LE often persists or recurs beyond the normal time for healing, it is recommended to give physical treatments to speed the recuperation of tendinopathy\(^10-11\). A prevailing notion in tendinopathy management is to regard exercise, load management as the key, and all other physical modalities being adjuncts to pain relief, and enhance the effects of exercise\(^6\). Over the past 10 years, acupuncture has gained wider acceptance for treating pain, by both clinicians and consumers of health care\(^12-13\). There is some evidence suggesting that acupuncture
treatment compared with sham acupuncture is effective in short-term relief of pain in LE\textsuperscript{14}. More recent studies supports that manual therapy, as in Mulligan’s Mobilization-with-movement (MWM), have a short-term relief of pain for patients with LE, and combined with eccentric exercise, it has a superior benefit over wait and see\textsuperscript{11,15}. At the time of planning the protocol, there were no published trials comparing acupuncture with manual therapy treatment of LE, in means of pain relief.

2 Objective of this study

The primary objective of the present study was to investigate the clinical effectiveness of acupuncture and manual therapy treatment of LE in an institute of sports medicine and rehabilitation. Such treatments were in addition to eccentric exercise and compared with eccentric exercise alone, during a 12-week follow-up.

2.1 Research question and hypotheses

In the process of developing the research question, we have explored the literature and previous articles on the topic of LE, because research questions arise most often from those that have been explored before.

“\textit{Is acupuncture or manual therapy treatment in addition to eccentric exercise, compared with eccentric exercise alone, assessed during a 12-week follow-up, useful means in pain relief for patients with LE?}”

2.1.1 Hypothesis for primary outcome

To describe the meaning of a statistically significant difference in pain relief for patients with LE receiving treatment in addition to eccentric exercise, either acupuncture or manual therapy compared to eccentric exercise alone, is the hypothesis of no significant difference (\(H_0\)).

\(H_0 = \text{there is no difference in pain relief between any of the groups.}\)
To determine the probability that the null hypothesis is true is an alternative hypothesis addressed later with specific tests \((H_1)\).

\[ H_1 = \text{at least one of the groups is significantly different from the remaining groups regarding the investigated population parameter.} \]

2.1.2 Hypothesis for secondary outcomes

To describe the meaning of a statistically significant difference in functional capacity of elbow and arm for patients with LE receiving treatment in addition to eccentric exercise, either acupuncture or manual therapy compared to eccentric exercise alone, is the hypothesis of no significant difference \((H_0)\).

\[ H_0 = \text{there is no difference in functional capacity of elbow and arm between any of the groups.} \]

To determine the probability that the null hypothesis is true is an alternative hypothesis addressed later with specific tests \((H_1)\).

\[ H_1 = \text{at least one of the groups is significantly different from the remaining groups regarding the investigated population parameter.} \]
3 Theory of this study

This chapter presents the theoretical framework of this study, based upon previous research. The etiology of LE is still not clear and systematic reviews have failed to draw any firm conclusions as to what treatment is most effective in managing this condition\textsuperscript{10-11}.

"A theory is a way of making sense of a disturbing situation"

Kaplan (1964)

3.1 Literature search

We have explored the literature and previous articles on the topic of LE. The searching strategies were Cochrane, for reviews on the pathology and management of LE. Further search in databases as PubMed, Medline, EMBASE and Pedro, for RCT’s which were not included in the systematic reviews. Using key words as:

“Lateral epicondylitis” OR “epicondylalgia” AND “acupuncture” AND “physical therapy” OR “physiotherapy” OR “manual therapy” and “lateral epicondylitis” OR “lateral epicondylalgia” AND “exercise” OR “eccentric exercise”

There were also additional search, after the planning of protocol, to include the latest research on the topic of management of LE.

3.2 Pathophysiology

Tendinopathy is a clinical descriptor for pain and pathology in and around tendons\textsuperscript{1}. Studies of tissue conducted via immunohistochemically analysis have revealed degenerative changes involving fibroblasts, blood vessels and collagen. The presence of angiofibroblastic hyperplasia and the absence of cell types involved in inflammation, confirm the tendinopathy diagnosis of LE\textsuperscript{5}. Of further importance, four stages of LE are described. In the first stage, there is a peritendinous inflammation, which is the active stage, associated with significant pain. Stages 2, 3 and 4 refer to the presence of angiofibroblastic degeneration, the last stage being more severe. Due to fibrosis of the tendon during stages two and three, it may rupture with further calcification in the last stage\textsuperscript{8-9}. Stage three and four have a poorer prognosis than the first and second of tendinopathy\textsuperscript{8}. 
3.2.1 Pain and neurochemical response

Despite the absence of inflammation, patients with LE experience pain, sometimes-severe pain, particularly with repetitive wrist movement or heavy activity involving hand gripping\(^1\). Studies have located sensory fibers containing substance-P and calcitonin gene related peptide (CGRP). The presence of these neuropeptides, which limited to a subgroup of small vessels, implies the possibility of neurogenic inflammation as a cause of the perceived pain by patients with LE\(^1\).

3.3 Diagnosis and assessment

LE is a diagnosis based on a clinical history and physical examination, and is characterized by the presence of pain over the lateral humeral epicondyle, that may radiate distally into the forearm. Palpation, gripping and resisted wrist and/or second or third finger extension, will further aggravate the pain\(^6\). Duration of symptoms and the number of recurrences may suggest either an acute injury, or condition consistent with a paratendinous inflammation (first stage) or later stages of tendinosis. Generally, symptoms duration less than three months would indicate an acute condition, while chronic condition would be consistent with duration longer than three months\(^8\text{-}^9\). To assist prognosis, assessment of pain and disability is necessary, and there is some evidence, which show that people, who present with severe pain and disability of arm at baseline, are more likely to have an ongoing pain at 12 months\(^5\text{-}^6\).

3.3.1 Clinical examination

A clinical examination consists often of several tests, like range of motion (ROM) of elbow and wrist and stress test of third finger and wrist extension\(^6\). Further, stress testing of the medial and lateral collateral elbow ligaments, and specific tests for elbow instability are normally assessed to aid the differential diagnosis of intra-articular and ligamentous pathology. The pain-free grip strength test is recommend, and ased with a dynamometer\(^17\). Clinicians are encouraged to be aware that there may be co-pathologies and an overlap in symptoms. Evaluation of the cervical and thoracic spine and neuro dynamic testing of the radial nerve may also be helpful in identifying spinal contribution to pain. While it is currently unclear as to what impact the presence of cervical and thoracic impairments have on the condition, exploratory research indicates that neck pain is more common among people with LE\(^6\text{-}^6\).
3.3.2 Diagnostic imaging
Diagnostic imaging, such as ultrasound (US) and magnetic resonance imaging (MRI) have high sensitivity, but lower specificity in detecting LE\textsuperscript{19}.

Structural abnormalities identified on imaging, tend to be consistent across all tendinopathies. More importantly, structural changes on imaging are present in approximately 50\% of healthy, asymptomatic age and gender matched individuals. Therefore, we must interpret these findings with caution\textsuperscript{19-20}. A notable differential diagnosis is the presence of a large tear (6mm) within the tendon or lateral collateral ligament, which is significantly associated with poorer prognosis for the patients with LE, and indicated greater likelihood of failing conservative management as physiotherapy including an eccentric exercise program\textsuperscript{20}.

3.4 Recommendations for the management of LE
Initial treatment for LE generally includes rest and pain relievers\textsuperscript{10-11}. There is conflicting evidence for the role of oral nonsteroidal anti-inflammatory medication in the management of LE. There is discussion on, that these drugs might be more appropriate for patients with active (first stage) or reactive rather than degenerative tendinopathy\textsuperscript{17}. There is strong evidence that corticosteroid medication proves short-term relief of pain but leads to worse outcomes after 6 and 12 months, compared to either a wait-and-see approach or physical therapy management\textsuperscript{11}. The exercise program is the most common treatment in the management of LE. Exercise has showed that it leads to greater and faster regression of pain, less sick leave and increased work ability\textsuperscript{22-23}.

3.4.1 Eccentric exercise
Exercise programs incorporating eccentric muscle activity are becoming increasingly popular, as they are likely to provide a more effective treatment than other forms of exercise therapy of LE\textsuperscript{22-23}. The optimal protocol of eccentric exercise program is still unknown\textsuperscript{21}. The effectiveness of the eccentric exercise program appears to be better when combined with other physical modalities, such as manual therapy\textsuperscript{22}.

\textit{Clinical principle of eccentric exercise}
In 1998, Alfredson\textsuperscript{24} performed, to our knowledge, the first study investigating the effects of eccentric exercise on diseased tendons. The protocol has since been used in most studies on
eccentric exercise\textsuperscript{23, 25}. The rationales of the effects of eccentric exercise compared to concentric exercise consist of three components, speed of movement, degree of musculotendinous stretch and muscular force or tension\textsuperscript{25-26}. With speed of movement, we refer to the time between biochemical response and to actual onset of muscular tension. This delay is shortest for the eccentric mode of contraction, which gives a potential training benefit\textsuperscript{25}. The opposite or antagonistic movement precedes the stretch part of movement in a rapid manner producing a subsequently greater magnitude of contractile force due to the addition of potential energy transferred from the series of elastic component. The eccentric contraction potentiates the force of the following concentric contraction. Further, eccentric muscle activity has maximum achievable tension level\textsuperscript{25-26}.

3.4.2 Eccentric exercise combined with other physical modalities
At the time of planning for this study, therapists and researchers were exploring a plethora of physical treatments in the management of LE. Given the complexity of the pathophysiology of LE, we propose a multimodal approach for the management of this condition. MWM in addition to eccentric exercise has a superior benefit over wait and see\textsuperscript{15}. Acupuncture compared with sham treatment is effective in short-term relief of pain in LE\textsuperscript{14}. Both acupuncture and manual therapy induce analgesia through several pain mechanisms, which enable exercise and load management, but there is little knowledge on the comparative effectiveness of manual therapy and acupuncture treatment of LE. Therefore, an explorative comparison of acupuncture and manual therapy treatment, in means of pain relief for patients with LE.

3.4.3 Acupuncture for pain relief
Over the past 10 years, acupuncture has gained wider acceptance for treating musculoskeletal disease, especially for the functional disability and pain symptoms\textsuperscript{1}. Acupuncture is known to induce analgesia via (or through) several pain mechanisms\textsuperscript{13}. The insertion of an acupuncture needle stimulates A-delta and C-fibers, and can result in the release of several neuropeptides involved in pain modulation and local vasodilation such as CGRP and substance P. This early work of Janzen and colleagues is testament to the historic belief that acupuncture may have the potential to optimize the body’s own natural healing response via a homeostatic mechanism\textsuperscript{27}. Recent research represented by Goldman\textsuperscript{28} states that acupuncture has a local anti-nociceptive effect, mediated by adenosine A1 receptors in muscle tissue triggered by the needle. In addition to pain relief; acupuncture has also shown the potential to increase local blood flow within a
target tissue and affect fibroblast migration through myofascial collagen stimulation, both important in attempting to recuperate tendinopathy.29-30.

3.4.4 Manual therapy and manipulation for pain relief

There is a growing body of literature reporting the effects and underlying mechanisms of joint manipulation in the management of LE.15 Evidence exists demonstrating that joint manipulation directed at the elbow and wrist as well, results in clinical alternations in pain and the motor system. The most used manipulation technique is MWM. It targets the common extensor tendon.16-17 The MWM technique is a non-thrust manipulation technique performed in the following fashion: the therapist first identifies a physical activity, which the patient reports to be painful. The patient is thereafter instructed to perform the identified painful task, while the therapist provides a laterally directed glide to the elbow.31-32 Preliminary findings have suggested that the orientation of the lateral glide and the amount of manual force applied by the therapist is critical to the effective application of this technique. Directing the lateral glide force posterior or directly lateral, is most effective.32 The therapist repeats this mobilization technique 6 to 10 per treatment session. The most important, is to repeat MWM as a part of a home exercise program, between physical therapy visits.15
4 Methods

In this chapter, methodology is presented. The design of this study, study population, recruitment plan, randomization and blinding, research ethics and interventions.

"Research methods are the particular strategies researchers use to collect the evidence necessary for building and testing theories"

Frey, Botan, Friedman, & Kreps (1991)

4.1 Study design

We designed this study as a pilot of a randomized controlled trial (RTC). It is a prospective as well as an experimental study, using primary data generated in the clinical environment. The design is three armed and single blinded. We choose an active control group, eccentric exercise alone, in order to explore the comparative difference of acupuncture versus manual therapy treatment of LE. Exercise alone, is also more ethical than just wait and see, and reasonable choice based upon research and clinical experience at NIMI. Therefore, all patients received eccentric exercise, being the cornerstone of rehabilitation of tendinopathy. The illustration of the study design is in figure 2.

Figure 2. Illustration of the design, three armed, with exercise alone as active control group.

4.1.1 Multi-arm design

The study design is three armed. Multi-arm design provides a way of substantially increasing the effectiveness of the clinical development process. With limited resources and patients, available, there is a need of alternative trials to maximize the number of treatments tested. Multi-arm designs are an important example of an alternative trial design that substantially improves efficiency over the traditional two-arm randomized RCT.\textsuperscript{34}
4.2 Study participants and recruitment

We recruited healthy subjects with LE through specialists in physical medicine and physiotherapists at the Norwegian Institute of Sports Medicine (NIMI) in Oslo. We also recruited subjects by advertising the study on NIMI’s web site and on Facebook. We advertised the study to widen our search for candidates with LE. Those who were suitable for enrollment were given an appointment for the medical practitioners to perform a clinical examination and screen eligible patients according to inclusion- and exclusion criteria. We enrolled the patient in the study if all inclusion and no exclusion criteria were met. Inclusion criteria were, age between 18 and 67 years, symptoms duration > two weeks, and average pain score of four or higher on a numeric rating scale (NRS; 0-10 where 0 = no pain and 10 = worst pain). Further, pain increase on palpation and resisted dorsiflexion of the wrist with the elbow extended and the fingers flexed and resisted radial deviation of the wrist, or resisted extension of the third finger. Exclusions criteria were: Corticosteroid injections during the last 4 weeks, bilateral symptoms, radio-ulna or radio humeral osteoarthritis, shoulder or neck disorders, diseases of the central or peripheral nervous system, inflammatory rheumatic diseases or unwilling to participate in the study.

The included patients completed a standard questionnaire prior to randomization, which covers patient demographics, level of education, occupation and previous cortisone injections. It is important to assess the individual factors that possibly may influence the treatment effect.

4.3 Randomization and blinding

We enrolled the patient in the study if all inclusion and no exclusion criteria were met. Only then the project leader was contacted, who allocated the patient to one of three treatment groups: eccentric exercise alone, acupuncture in addition to eccentric exercise or manual therapy in addition to eccentric exercise. The randomization was organised with a 1:1:1 ratio and in blocks of six. Patients drew a sealed opaque envelope with disclosure of group allocation from a collection of at least six envelopes.
4.4 Research ethics

The regional Committees for Medical Research Ethics in southeast Norway (REK Sør-Øst B) (ref.nr 2014/1520) approved the project before the start of trial (appendix 1 and 2). REK are monitoring all health research committed in Norwegian health institutions. The Norwegian Centre for research Data (NSD) also approved the project (appendix 3). The trial adheres to the principle of the Declaration of Helsinki, and to the CONSORT guidelines for transparent reporting of trials36.

4.4.1 Informed consent

One common principle of research ethics is that of voluntary consent of the individual participating in the research. Informed consent requires that the patients give permission for treatment, as well as adequate information in order to make educated decisions about undergoing the treatment37-38. To ensure the quality of consent in this trial, the project leader was handling the important issues of the informed consent. All patients signed the written consent-form entailing information concerning the study, prior to inclusion and randomization (appendix 4).

The project leader informed the patients that they had the right to withdraw from the study at any time. Further, that all information gathered was anonymous, and kept concealed throughout the entire study. We will destroy the data, when the study is finished and the article is accepted for publication. The patients in the treatment groups, paid for the number of treatment sessions attended, as under usual circumstances in a clinical setting.

4.5 Interventions

Based upon previous research 22-23, 39 and clinical experience with management of LE, we choose to give all patients instruction in the same eccentric exercise program. In addition to eccentric exercise, two groups received either acupuncture or manual therapy treatment for pain relief. The theory is that treatment of pain (like applying acupuncture or MT in addition to exercise) will enhance the effects of exercise, and therefore the recuperation of tendinopathy15, 17. The interventions in this study are depicted in the article. Numbers of treatment sessions in both acupuncture and manual therapy group consisted of minimum three and maximum eight treatments. The patients received their first treatment within one week from randomization, and the following treatments sessions within eight weeks.
4.5.1 Eccentric exercise program
We searched through previous research, but the optimal protocol of eccentric exercise program is still unknown\textsuperscript{22-23}. Therefore, we did discuss with experienced physiotherapists at NIMI, how to design the eccentric exercise program in this study. Depicted consensus of how to perform the eccentric exercise program for LE is in an attached brochure (appendix 5).

4.6 Primary and secondary outcomes
The primary outcome of this study was \textit{pain relief} for patients with LE, assessed with numeric rating scale (NRS).

Secondary outcomes were \textit{functional capacity of elbow and arm}, assessed with Quick-DASH, number of treatment sessions, sick listing, analgesics management, patient satisfaction with treatment and global perceived effect.
5  Clinical outcomes

Clinical outcomes intend to provide a score, which represent some aspect of the patients health status. We wanted to determine the clinical effectiveness for patients with LE, when exposed to different treatment modalities. The effectiveness of treatment needs to be meaningful for the patient, which in itself is a positive effect on how the patients feel (pain) and how they function.

All outcomes are standardized and validated patient reported outcome measures (PROMs). The clinical outcome data at baseline was collected before randomization, in order to minimize the distorting effect of the fact that they were not able to choose which group to attend to, or which treatment modality they preferred.

Primary PROMs at baseline (pretest), week 1, 2, 3, 4 and 12 after start of treatment. Secondary PROMs at baseline (pretest), week 4 and 12 after start of treatment.

5.1  Primary outcome

5.1.1  Elbow pain on Numeric Rating Scale (NRS)

To assess the intensity of elbow pain, the patients rated their pain on a NRS (an interval scale). The NRS consist of a range of numbers between 0 and 10, with the smaller numbers indicating less pain. The patients were asked to rate their elbow pain by indicating a number between 0 and 10. Multiple scales at given time points, to distinguish between present, worst and lesser pain during the last week, an average were calculated. The NRS assessment tool is valid and a reliable method of measuring patients perceived pain. The primary outcome was the differences in NRS score (pain relief) between the treatment groups and exercise alone, based upon the primary hypothesis. Further, there were an explorative comparison of difference in pain relief between acupuncture and manual therapy treatment.

5.2  Secondary outcomes

5.2.1  The disabilities of the arm shoulder and hand (DASH)

We measured functional capacity of elbow and arm by using the questionnaire DASH. The DASH consists of 30 questions, designed to measure symptoms, function and working
capacities. The DASH tool is a valid and reliable method of measuring patient function or dysfunction of upper extremities. The study result supports that DASH is a reliable and valid instrument to measure functional disability and to investigate the ergonomic risk factors, working with upper-extremity musculoskeletal complaints. From the original DASH a shorter version, the 11-item Quick DASH, is developed. Study results indicate that the Quick DASH can be used instead of the DASH with similar precision in upper extremity disorders. Hence, we used the Quick DASH in this study. The secondary outcomes was the differences in Quick-DASH score, between the treatment groups and exercise alone, based upon the primary hypothesis. Further, there were an explorative comparison of difference in functional disability between acupuncture and manual therapy treatment.

5.2.2 Number of treatment sessions
Number of treatment sessions in both acupuncture and manual therapy group consisted of minimum three and maximum eight treatments. The intensity of perceived pain from the participants was taken into consideration by the practitioner’s. The number of treatment sessions was registered by the therapists, and verified in the patient’s record. The outcome was the differences in number of treatment sessions between acupuncture and manual therapy group.

5.2.3 Sick listing
Patients reported days of sick leave during the intervention period, with a 12-week follow-up.

5.2.4 Analgesics mangement
The patients were asked to report their use of analgetics, type and dosage during the intervention period, with a 12-weeks follow-up.

5.2.5 Patient’s satisfaction
Two Likert scales (5-point and 7-point) evaluated patient satisfaction with treatment and global perceived effect, at last follow-up.
6 Sample size and statistical methods

The aim of any clinical research is to have large enough sample size to detect the actual difference between two groups (power) and to provide an estimate of the difference with a reasonable accuracy or precision. Further, to calculate the sample size which is the number of patients needed to be included in a study to answer the research question47.

6.1 Sample size calculation

The primary outcome of this study is pain relief (continues variable). The primary hypothesis of this study is that clinical outcomes will be equal in patients receiving treatment in addition to eccentric exercise, either acupuncture or manual therapy, compared to eccentric exercise alone. Before the calculations, we chose a significance level of .05, meaning that there is less than 5 % chance for drawing a false-positive conclusion (type 1 error), and the power of estimates to be 90 %. The power represents the chance of avoiding a false-negative conclusion (type 2 error)48-49. Then, based on former publications, we decided the minimal important change (MIC) of pain to be a reduction of two points on NRS50. In conclusion, we based the sample size calculation for a full-scale trial on the ability to detect a NRS change score of -2.0. We estimated the target sample size to be 30 persons per group (90 % test power and two-sided test with significance level of .05) giving 90 persons to detect a clinically meaningful difference of a NRS change score of -2.0. To allow for loss to follow-up, the sample size should be increased by 10 % to 99 (33 per group). However, we designed this present study as a pilot and each group included only 12 participants51.

6.2 Statistical Method

We analyzed all data in Statistical Program for Social Sciences (SPSS), version 22. The data collected in this study consisted of both continues and categorical variables. We checked continues variables for normal distribution, and thereafter analyzed with parametric and non-parametric methods which ever was appropriate. Primary and secondary outcomes were analyzed group wise, at given time points.

The differences between groups (both at given time points) were assessed using mixed model analysis for repeated measurements. All available data were analyzed using linear mixed models for repeated measures, with unstructured covariance matrix to model dependencies.
within individuals assessed at multiple time points. A mixed model allows assessing possible differences between groups, adjusted for selected covariates and when all time points are considered. In addition, the estimated differences between groups can be calculated for given time points. The selected variables included in the model were age, gender, level of education, outcome and time. Further, the estimated overall means were presented with 95% confidence intervals (CI). All statistical tests were two-sided. $P < 0.05$ was considered as statistically significant. As our study is a pilot study, our results were considered as exploratory and no correction for multiple testing was performed.
Clinical comparative effectiveness of acupuncture versus manual therapy treatment of lateral epicondylitis: a pilot for a randomized controlled trial

Katrine Bostrøm, Sverre Mæhlum, Milada Cvancarova Småstuen, Kjersti Storheim

ABSTRACT

Background: Lateral epicondylitis (LE) or tennis elbow is the most common chronic musculoskeletal pain condition affecting the elbow. Physical therapies are recommended for the management of LE. Manual therapy (elbow mobilization), in addition to eccentric exercise has a superior benefit over wait and see. Acupuncture compared with sham treatment is effective in short-term relief of pain in LE, but there is little knowledge on the comparative effectiveness of manual therapy and acupuncture treatment of LE, in means of pain relief.

Objective: The aim of the present study was to investigate the clinical effectiveness of acupuncture and manual therapy treatment of LE in addition to eccentric exercise, compared with eccentric exercise alone assessed during a 12-week period.

Methods: A pilot for a randomized controlled trial was conducted in the city of Oslo, Norway. We included 36 women and men with clinically diagnosed LE, and randomly assigned the patients to one of the three treatments: eccentric exercise alone, acupuncture or manual therapy in addition to eccentric exercise.

Results: The differences in mean score pain relief were statistically significant for treatment groups compared to the exercise alone, all measurements in time considered. Further, the acupuncture group was highly significantly different from the exercise alone group (p<0.001). However, this difference in estimated mean scores was only borderline significant when compared with the manual therapy (all measurements considered). Patients in exercise alone had significantly higher mean pain score than patients in treatment groups, the estimated mean pain score for exercise alone (all measurements considered) with 95 % CI was 4.04 [3.56; 4.51], and 2.82 [2.46; 3.18] for acupuncture and 3.37 [2.88; 3.86] for manual therapy group.

Conclusions: Patients receiving treatment in addition to eccentric exercise, either acupuncture or manual therapy, experienced a better pain relief than those receiving eccentric exercise alone, during treatments and up-to 12-week follow-up.

Trial registration: NCT02321696
Introduction

Work-related upper extremity disorders are common problems in working populations in western countries. These include a range of symptoms and afflictions related to the neck, shoulder, elbow or hand\(^1\). Lateral epicondylitis (LE) or tennis elbow, is the most common chronic musculoskeletal pain condition affecting the elbow\(^2\). The annual incidence is four to seven cases per 1000 patients in general practice, and as high as 17% of workers in highly repetitive hand task industries\(^3\). It is a painful condition, leading to loss of function of the affected limb. Therefore, it can have a major impact on the patient's work and personal life. LE persists for an average of six to 24 months. It is further associated with significant sickness absence in 5% of affected working-aged adults\(^2\). The cost is therefore high, both in terms of loss of productivity and health care utilization.

For some time, it was suggested that LE involved an inflammatory process, hence the name. Consistent absence of inflammatory cells has resulted in the consensus that the process is non-inflammatory in nature, and reconsidered as degenerative\(^1\). The main theory is that LE is caused by the incomplete repair of repetitive micro-trauma of the common extensor tendon tissue attached to the lateral epicondyle of the elbow, as in tendinopathy\(^1,5\). Since LE often persists or recurs beyond the normal time for healing, it is recommended to give physical treatments to speed the recuperation of tendinopathy\(^5-6\). A prevailing notion in tendinopathy management is to regard exercise and load management as the key, and all other physical modalities being adjuncts to give pain relief and enhance the effects of exercise\(^6\). There is some evidence that eccentric is superior to concentric exercise\(^7-8\).

Despite decades of research, investigating physical treatments and the underlying mechanisms of LE, it remains a challenging condition for clinicians\(^1,5\). Physiotherapy is the most common treatment for LE, but research has not yet proven superiority of one specific approach. In general, treatments like external support, stretching, soft tissue mobilization, acupuncture and strengthening exercises are recommended\(^9\).

Over the past 10 years, acupuncture has gained wider acceptance for treating pain, by both clinicians and consumers of health care\(^10\). Acupuncture is known to induce analgesia via/or through several pain mechanism\(^11\). There is some evidence suggesting that acupuncture treatment compared with sham acupuncture is effective in short-term relief of pain for patients.
with LE\textsuperscript{12}. Research on physiotherapy treatment supports that manual therapy techniques (mulligan’s mobilization with movement) have a short-term relief of pain for patients with LE, and combined with eccentric exercise it has a superior benefit over wait and see\textsuperscript{13-14}. At the time of planning the protocol, there were no published trials comparing acupuncture with manual therapy treatment of LE, in means of pain relief, and very few interventions have shown consistent effectiveness over other. It appears to be a lack of evidence for between-intervention superiority.

The aim of the present study was to explore the clinical effectiveness of acupuncture and manual therapy treatment of LE, in addition to eccentric exercise. As a control group, we decided to use eccentric exercise alone, which is a reasonable option according to clinical practice and research. Therefore, all patients received eccentric exercise, being the cornerstone of rehabilitation of tendinopathy.

**Objectives**

The primary objective of the present study was to investigate the clinical effectiveness of acupuncture and manual therapy treatment of LE in an institute of sports medicine and rehabilitation. Both treatments were in addition to eccentric exercise, compared with eccentric exercise alone assessed during a 12-week follow-up.

**Methods**

**Trial design and setting**

To prepare for a full-scale trial, a pilot of a randomized controlled trial was conducted in a private health care setting (NIMI) in Oslo, Norway. The design is three armed and single blinded. The trial adheres to the principle of the Declaration of Helsinki\textsuperscript{15}, and to the CONSORT guidelines for transparent reporting of trials\textsuperscript{16}. The regional Committees for Medical Research Ethics in southeast Norway (Rek Sør-Øst B) (ref.nr 2014/1520) approved the project before start of the trial, and reported to Norwegian Centre for Research Data (NSD). All patients gave their written informed consent.
Participants
Adults aged 18-67 years seeing their physiotherapist or medical doctor at NIMI with pain from the lateral part of the elbow were screened for eligibility. The pain had to be reported by the patients with an intensity of four or higher on a numeric rating scale (NRS; 0-10). Further inclusion criteria were pain on palpation, and increased pain on resisted dorsiflexion of the wrist with the elbow extended and the fingers flexed, and resisted extension of the third finger. To avoid light, self-limiting conditions to be included, we pragmatically chose to exclude patients with less than 2 weeks symptom duration. Other exclusion criteria were treatment with corticosteroid injection within the last 4 weeks, bilateral symptoms, radio-ulna or radio humeral osteoarthritis, neck or shoulder problems, inflammatory rheumatic diseases, disease of the central or peripheral nervous system, or unwillingness to participate in the study.

Interventions
In a 12 weeks treatment period, patients received one of three treatments: eccentric exercise alone, acupuncture in addition to eccentric exercise or manual therapy in addition to eccentric exercise.

The group of eccentric exercise alone was instructed once (at the day of randomization) and did not receive any additional intervention (just wait and see). Patients in the acupuncture and manual therapy groups received their first treatment within one week after randomization. During a period of 8 weeks, they had a minimum of three, and a maximum of eight treatment sessions, depending on the patients’ perceived intensity of pain and the therapists’ clinical evaluation. All groups received the same information and advice, including the natural course of the condition and expected duration of symptoms. Patients were encouraged to use their arm normally, but to avoid carrying heavy loads and pain-provoking activities as gripping and repetitive wrist movement.

Eccentric exercise
We instructed all patients to follow an eccentric exercise program for LE, to strengthen the extensor muscles and tendon. Strengthening exercise is a common treatment in physical rehabilitation of tendon problems\(^{17}\). To gain maximum effect of exercise, the starting weight should have been individually tailored, but to simplify clinical application, the starting weight
in this study was standardized. They were told to increase load once a week, with 10% of starting weight, or less, if the pain intensified. We also gave them a written instruction on how to perform this exercise. The patients were encouraged to do their exercise at home, on a daily basis from enrolment and 12 weeks forward. Further, a secretary of NIMI gave all patients included a weekly text message as a reminder to do their daily exercise at home.

**Acupuncture**

An acupuncturist with 12 years of clinical experience performed all the acupuncture treatments, according to traditional Chinese methods.

For the acupuncture in this study, we gave a generalized treatment, consisting of selected points, which were recommended by an expert panel for the treatment of LE. As local points, we selected LI11 and LI10 over the muscular origin of the lateral extensor group of the forearm, and LU5 in the cubical region. As distal points, we selected LI4 and TE5 for the treatment of pain in the upper limb, and GB34 for treatment of tendinitis in general, and ST36 for treatment of pain. The acupuncturist inserted the needles down to the musculature, approximately 15 mm in depth, and obtaining De Qi sensation. All the points, except ST36 were manipulated with a reducing technique to obtain pain relief. The needles remained in situ for 20 min.

**Manual therapy**

Two physiotherapists with specific manual therapy qualifications performed all the manual therapy sessions, according to evidence-based physiotherapy. The practitioners had long clinical experience.

The manual therapy techniques consisted of Mulligan’s Mobilization-with-movement (MWM). The manual therapist performed a lateral glide with gripping, a posterior-anterior glide on the radial head with supination of the radio-ulnar joint, and a lateral gapping manipulation technique. The mobilization techniques consisted of eight repetitions in a session of three. The aim was to provide short-term pain relief thus facilitating pain free exercise.
Outcomes

All outcomes are standardized and validated patient reported outcome measures (PROMs). Further, clinical outcomes at baseline were measured before randomization. Data were collected electronically.

Primary PROMs at baseline (pretest), week 1, 2, 3, 4 and 12 after start of treatment. Secondary PROMs at baseline (pretest), week 4 and 12 after start of treatment.

The included patients completed a standard questionnaire prior to randomization, which covers patient demographics, level of education, occupation and previous cortisone injections.

Primary outcome

Numeric rating scale (NRS)

The primary outcome of this study was pain relief\(^2\). The patients used a NRS to assess the intensity of their elbow pain. The NRS consist of numbers between 0 and 10, with the smaller numbers indicating less pain. Multiple scales at given time points, to distinguish between present, worst and lesser pain during the last week, an average were calculated. The NRS assessment tool is found to be valid and a reliable method of measuring patients perceived pain\(^2\)\(^3\).

Secondary outcomes

The disabilities of the arm shoulder and hand (DASH)

Secondary outcomes measures included functional capacity of elbow and arm, assessed with Quick-Dash, which is a shorter version of the original DASH\(^2\)\(^4\). Study results indicate that the Quick-DASH can be used instead of the original DASH with similar precision in upper extremity disorders\(^2\)\(^5\).

Patients were also asked to report days of sick leave and use of analgesics, and they reported their satisfaction with treatment and global perceived effect at the last follow-up\(^2\)\(^6\). The therapists reported the number of treatment sessions and verified it in the patient’s record.
Sample size calculation

The primary hypothesis of this study is that clinical outcomes will be equal in patients receiving treatment in addition to eccentric exercise, either acupuncture or manual therapy, compared to eccentric exercise alone. Sample size calculation for a full-scale trial was based on the ability to detect a minimal important change (MIC) NRS score of -2.0, which is clinically relevant based on previous studies. We estimated the target sample size to be 30 persons per group (two-sided test with 90% power and significance level of .05), in total 90 persons. To allow for loss to follow-up, the sample size should be increased by 10% to 99 (33 per group). However, we designed this present study as a pilot and each group included only 12 participants.

Randomization and blinding

One of the trial medical doctors or a physiotherapist first screened patients for eligibility. We enrolled the patient in the study if all inclusion and no exclusion criteria were met. Only, then was the project leader contacted, who allocated the patient to one of three treatment groups: eccentric exercise alone, acupuncture in addition to eccentric exercise, or manual therapy in addition to eccentric exercise. The randomization was organised in blocks of six with a 1:1:1 ratio. Patients drew a sealed opaque envelope with disclosure of group allocation from a collection of at least six envelopes.

Statistical methods and analysis

We analyzed all data in Statistical Program for Social Sciences (SPSS), version 22. Primary and secondary outcomes were analyzed group wise, at given time points. Differences between groups were assessed both at given time points and when all measurements were considered. All available data were analyzed using linear mixed models for repeated measures, with unstructured covariance matrix to model dependencies within individuals assessed at multiple time points. Mixed models allow assessing possible differences between groups, adjusted for selected co-variates and when all time points are considered. In addition, the estimated differences between groups can be calculated for given time points. The model was adjusted for possible confounders as age, gender, level of education, outcome and time. Further, the estimated overall means were presented with 95% confidence intervals (CI). All statistical tests
were two-sided. \( P < 0.05 \) was considered as statistically significant. As our study is a pilot study, our results were considered as exploratory and no correction for multiple testing was performed.

**Results**

**Recruitment and participant flow**

Fifty patients were referred to the study between March 2015 and April 2016. Of these, 14 were excluded (12 did not meet the inclusions criteria, and two declined to participate). Hence, 36 patients were included and randomized in the study. The trial was completed in August 2016, with 28 (78%) patients completing all measurements including last follow-up at 12 weeks after start of treatment. **Figure 1** summarizes the patient flow.

In total, 13 patients were randomized to treatment with acupuncture, 12 to manual therapy and 11 to eccentric exercise alone. All patients received allocated treatment. Patients in acupuncture and manual therapy group concluded the treatment in accordance with protocol (having attending at least 3 of maximum 8 treatment sessions). Eleven (85%) patients in the acupuncture group completed the last follow-up, compared to nine (75%) patients in manual therapy group, and 8 (73%) in the exercise alone.
Baseline data

Before randomization, baseline characteristics of study population were registered (table 1). The groups were similar regarding mean age, work status and overall severity of symptoms; however, a higher proportion of patients in the manual therapy group was males, had higher education and worked in the office compared to the other two groups. The patients in exercise alone group had a higher level of mean pain scores at baseline, compared to the other two groups.

Figure 1. Flow-diagram showing recruitment, randomization and follow-up rates in this present pilot.
Table 1. Characteristics of the study population at baseline. Values are numbers (percentage) unless otherwise stated.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Exercise alone</th>
<th>Acupuncture</th>
<th>Manual therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Year)</strong></td>
<td>Mean (SD)</td>
<td>49 (11)</td>
<td>47 (3)</td>
<td>51 (4)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (42)</td>
<td>6 (55)</td>
<td>6 (46)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Higher education*</td>
<td>29 (81)</td>
<td>8 (73)</td>
<td>10 (76)</td>
<td>11 (92)</td>
</tr>
<tr>
<td><strong>Type of work</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Manual</td>
<td>12 (33)</td>
<td>5 (45)</td>
<td>5 (38)</td>
<td>2 (16)</td>
</tr>
<tr>
<td>- Office</td>
<td>24 (67)</td>
<td>6 (55)</td>
<td>8 (62)</td>
<td>10 (83)</td>
</tr>
<tr>
<td><strong>Work status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Paid work</td>
<td>30 (82)</td>
<td>10 (90)</td>
<td>10 (77)</td>
<td>11 (92)</td>
</tr>
<tr>
<td>- Sick leave</td>
<td>2 (6)</td>
<td>-</td>
<td>1 (8)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>- Student</td>
<td>2 (6)</td>
<td>1 (9)</td>
<td>1 (8)</td>
<td>-</td>
</tr>
<tr>
<td>- Retired</td>
<td>1 (3)</td>
<td>-</td>
<td>1 (8)</td>
<td>-</td>
</tr>
<tr>
<td>- Unemployed</td>
<td>1 (3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Previous treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Cortisone injections</td>
<td>6 (17)</td>
<td>1 (9)</td>
<td>2 (15)</td>
<td>3 (25)</td>
</tr>
</tbody>
</table>

| Pain intensity**             | Mean (SD) | 4.3 (1.3) | 4.8 (1.3) | 3.9 (1.3) | 4.1 (1.3) |
| Functional capacity of arm***| Mean (SD) | 30.5 (14.2)| 29.2 (14.4)| 30.5 (14.2)| 31.7 (15.2)|

* College or university degree (3 years or more).
** NRS (0-10). 0 = no pain, 10 = worst pain. Unadjusted mean.
*** Quick-DASH (0-100). A higher score indicates a greater disability. Unadjusted mean.

Outcomes and estimations

Primary outcome

Adjusted mean pain scores estimated with 95 % CI at all follow-up time points, are listed in table 2. The acupuncture and manual therapy group showed a gradual and very similar pattern of pain relief, while exercise alone showed less improvement. Patients in exercise alone had significantly higher mean pain score than those in treatment groups, the estimated mean pain score for exercise alone (all measurements considered) with 95 % CI was 4.04 [3.56; 4.51], and 2.82 [2.46; 3.18] for acupuncture and 3.37 [2.88; 3.86] for manual therapy group. The pattern of change in pain intensity from baseline and up to last follow-up for all groups is depicted in figure 2.
When assessing the individual time points, our data revealed a slight worsening of symptoms at week 3, in exercise alone and acupuncture group, more dominantly in exercise alone. The estimated mean pain score for exercise alone with 95 % CI was 4.02 [2.87; 5.18] at week two compared to 4.27 [3.25; 5.30] at week three. At 12 weeks, the mean pain scores were comparable in treatment groups, but worse in exercise alone (table 2).

**Table 2.** Adjusted mean scores of pain intensity and functional capacity of arm, estimated with 95 % CI, at each follow-up.

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Follow-up</th>
<th>Exercise alone</th>
<th>Acupuncture</th>
<th>Manual therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain score</strong>*</td>
<td>Baseline</td>
<td>4.38 [3.62; 5.15]</td>
<td>3.96 [3.29; 4.64]</td>
<td>4.47 [3.72; 5.22]</td>
</tr>
<tr>
<td></td>
<td>1 week</td>
<td>4.22 [3.28; 5.16]</td>
<td>2.97 [2.16; 3.77]</td>
<td>4.02 [3.08; 4.97]</td>
</tr>
<tr>
<td></td>
<td>2 week</td>
<td>4.02 [2.86; 5.17]</td>
<td>2.81 [1.86; 3.76]</td>
<td>3.52 [2.42; 4.63]</td>
</tr>
<tr>
<td></td>
<td>3 week</td>
<td>4.27 [3.25; 5.29]</td>
<td>2.85 [2.04; 3.66]</td>
<td>3.12 [2.20; 4.05]</td>
</tr>
<tr>
<td></td>
<td>4 week</td>
<td>3.80 [2.74; 4.85]</td>
<td>2.52 [1.62; 3.41]</td>
<td>3.03 [2.02; 4.04]</td>
</tr>
<tr>
<td></td>
<td>12 week</td>
<td>3.49 [2.34; 4.64]</td>
<td>1.79 [0.89; 2.70]</td>
<td>2.03 [0.86; 3.20]</td>
</tr>
<tr>
<td><strong>Function of arm</strong>**</td>
<td>Baseline</td>
<td>31.54 [22.10; 40.98]</td>
<td>33.72 [25.44; 41.99]</td>
<td>37.24 [27.89; 46.59]</td>
</tr>
<tr>
<td></td>
<td>4 week</td>
<td>35.41 [25.35; 45.47]</td>
<td>28.69 [20.38; 37.00]</td>
<td>28.73 [18.92; 38.55]</td>
</tr>
<tr>
<td></td>
<td>12 week</td>
<td>30.00 [19.96; 40.04]</td>
<td>19.81 [11.99; 27.63]</td>
<td>16.08 [05.56; 26.60]</td>
</tr>
</tbody>
</table>

* NRS (0-10). 0 = no pain, 10 = worst pain.
** Quick-DASH (0-100). A higher score indicates a greater disability.

To compare groups statistically, estimated marginal means for pain relief, adjusted for covariates; as age, gender, level of education, outcome and time were analyzed with a linear mixed model. The result of the analyses was significant for differences in mean score pain relief for treatment groups compared to exercise alone, all measurements considered. Further, the acupuncture group was highly significantly different from the exercise alone group (p<0.001). However, this difference in estimated mean scores reached only the level of borderline significance when compared with the manual therapy (all measurements considered). The presentation of pairwise comparison of all groups is in table 3.

Further, our data revealed that individuals with the highest level of education always had significantly lower levels of pain, compared to those with the lowest level of education. In addition, a gender difference emerged.
Table 3. Pairwise comparisons (groups) of mean difference in pain intensity, all measurements considered.

<table>
<thead>
<tr>
<th>Pairwise comparisons of groups</th>
<th>Mean difference*</th>
<th>SD</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual therapy compared with acupuncture</td>
<td>0.55</td>
<td>0.28</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Exercise alone compared with acupuncture</td>
<td>1.21</td>
<td>0.27</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Exercise alone compared with manual therapy</td>
<td>0.67</td>
<td>0.30</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

* NRS (0-10); 0 = no pain, 10 = worst pain.
** Adjusted for multiple comparisons.

Secondary outcomes

Adjusted mean scores of functional capacity of elbow and arm estimated with 95 % CI at all follow-up time points are listed in table 2. The acupuncture and manual therapy group showed a gradual and very similar pattern of improvement in functional capacity of elbow and arm, while exercise alone only had less improvement. Patients in exercise alone had higher levels of disability of elbow and arm than treatment groups, the estimated mean score of functional capacity of arm for exercise alone (all measurements considered) with 95 % CI was 32.31 (25.94; 38.69) and 27.40 (22.48; 32.33) for acupuncture and 27.35 (20.61; 34.09) for manual therapy.

When assessing the individual time points, our data revealed a slight worsening of symptoms for patients in exercise alone group at week 4, compared to baseline, but better in acupuncture and manual therapy group. The estimated mean functional capacity score for exercise alone with 95 % CI was 31.54 [22.10; 40.98] at baseline compared to 35.41 [25.35; 45.47] in week four. At 12 weeks, the mean scores were comparable between acupuncture and manual therapy group, but worse in exercise alone (table 2). The estimated marginal mean was 21.97 [15.90; 28.03] at last follow-up compared to 34.17 [28.53; 39.80] at baseline. Overall, all measurement considered, all participants have improved their arm function; however, our data did not reveal any between-group differences. Further, individuals with the highest level of education always had significantly higher functional capacity of arm (p < 0.05) compared to those with the lowest level of education.
Number of treatment sessions
The mean number of treatment sessions attended with 95% CI was 3.92 [2.98; 4.86] for acupuncture group and 4.33 [3.17; 5.49] for manual therapy group. The majority of participants (64%) in both treatment groups received only three treatment sessions, which was the minimum number required in the trial (maximum of eight); the reasons included non-attendance, or recovery of pain.

Patient satisfaction
The patients were asked to report their satisfaction with treatment at last follow-up. Twenty-five (69%) patients answered these questions and 21 (84%) of those, were satisfied with treatment. Only one (4%) patient was not satisfied, and three (12%) were indifferent.

Further, they were asked to report how much that their condition has improved or deteriorated since start of treatment (global perceived effect). The majority of all patients reported that they were improved in their condition; two (6%) patients in the acupuncture group reported a complete recovery, compared to exercise alone, were one (3%) patient reported that he or she was worse.

Sick leave and use of analgesics management
Two (5%) of the included 36 patients were on sick leave at baseline. They were back to paid work within four weeks. One patient had 12 full days of sick leave and the other had 50% for four weeks. Further, few patients used analgesics during the trial period. Six (17%) patients used analgesics due to pain from their elbow at baseline. They had a mean of 12 days during last four weeks before enrollment. Four weeks after enrollment there were seven (19%) patients using analgesics, with a mean of 12 days. At 12 weeks, only three (8%) patients used analgesics, with a mean of 17 days during last eight weeks.
Discussion

Patients receiving treatment, either acupuncture or manual therapy, in addition to eccentric exercise, had a better pain relief than those receiving eccentric exercise alone, all measurement considered. The result though, revealed less homogeneous outcomes than we expected from the different treatment modalities. The acupuncture group was significantly and highly different from the exercise alone group (p<0.001). However, this difference in estimated mean scores reached only borderline significance when compared with the manual therapy (all measurements considered).

There was a slight increase in pain intensity for patients in exercise alone at week three, compared to week two. When patients do strength exercise, this is to be expected. The increases in load on tendon will possible give some irritation, before the tissue begins to repair. Another consideration is that the initial response, pain relief between baseline and week two might have led patients to return to normal activity too soon, and therefore an increase in pain intensity due to over use of arm. Further, there is of importance to consider the difference in compliance of exercise between treatments groups and exercise alone. We expect a higher compliance of
exercise in the treatments group, because of the therapeutic-patients relations. When receiving additional treatment and interact with the therapist in a clinical setting the possibility of executing your exercise program at home is higher, from a clinical perspective.

The significant difference in mean pain relief score for treatment groups, compared to exercise alone, indicate that there were a possible added effect of acupuncture or manual therapy treatment of LE in addition to eccentric exercise. The pattern of effect seems to follow the theory that pain relief could enhance the effect of exercise and/or speed the recuperation of tendinopathy\textsuperscript{6}. Both acupuncture and manual therapy induce analgesia through several pain mechanisms, which enable exercise and load management. In addition to pain relief; acupuncture has also shown the potential to increase local blood flow within a target tissue and affect fibroblast migration through myofascial collagen stimulation, both important in attempting to recuperation of tendinopathy\textsuperscript{29}.

During acupuncture or manual therapy treatment, patients do not only benefit from the specific treatment itself, the needling or the manipulation techniques, but also from the non-treatment specific agents, the so-called placebo effects or contextual effects\textsuperscript{6}. Patient’s pain relief is therefore a results from a combination of specific treatment agents, and non-treatment specific agents. Important non-specific agents can be; spontaneous remission, expectancy, motivation and other psychosocial agents as therapeutic-patients relations\textsuperscript{6}. It is of importance to take into consideration the non-treatment specific effect, when discussing our results. Thus, treatment groups reported a significant higher mean score of pain relief (all measurements considered) than exercise alone, some of the pain relief could be explained by the non-treatment specific effect. It is expected that all groups could experience spontaneous remission during the period of trial, but expectancy, motivation and the therapeutic-patients relations could be of importance and bias to the result.

While some studies investigate treatment effects as early as after last treatment session, our study let several weeks pass before measuring post treatment effects. Even though follow-up investigations help understand a longer-term effect of a therapy, a prolonged period of between the end of a treatment and the assessment of its effectiveness may distort results.
Harms

There were no participant’s reports of adverse advents or harms. Acupuncture and manual therapy are considered safe treatments, and are among the most common physical interventions for pain relief.

Strengths and limitations

A major strength of this study is the fact that the patients were recruited among tennis elbow patients in a health care center, specialized in sports medicine and rehabilitation of musculoskeletal conditions. Although this was not a random sample from this patient population, it may be regarded as fairly representative of this type of patients in the general population. There were relative few dropouts. Clearly defined inclusion criteria and the fact that all patients treated at the selected clinic had a possibility to participate enabled us to generalize the results. Open inclusion criteria, made it easier to generalize the result. The patients were not blinded to either acupuncture or manual therapy treatment, and that may have influenced outcomes. To gain maximum effect of exercise, the starting weight should be individually tailored, but to simplify clinical application, the starting weight in this study was standardized. We did not log or supervise the home exercise, but all participants received a text message every week, as a reminder to do his or her exercise program. Reminding the participants to do their exercise, is often used in clinical practice, and may possibly better the compliance in this study.

Differences to other studies

Our findings were similar to other recently published studies and systematic reviews, which have found a short-time effect of manual therapy in addition to eccentric exercise. The difference to other studies is that acupuncture in addition to eccentric exercise, also had a significant effect, in means of pain relief. To our knowledge, there is only one other prospective, randomized control trial, which compare manipulation technique with acupuncture treatment alone, which was published after the present study was commenced. Hsu et al. found that manipulation technique improved pain in patients with LE, during the first few treatments and up-to 8-week follow-up, better than acupuncture. In contrast, our study found no differences between manual therapy and acupuncture in pain relief, during treatments and up-to 12-week follow-up.
Conclusions and implications

In conclusion, patients receiving treatment, either acupuncture or manual therapy, in addition to eccentric exercise, experienced a higher mean pain relief score than those receiving eccentric exercise alone, during treatments and up-to 12-week follow-up.

The effectiveness of alternative pain relief such as acupuncture in people with LE is worthy of further investigation.

There is a need to clarify the role of exercise in managing LE, including optimal dosage and type of exercise. Bearing that in mind, exercise being the cornerstone of rehabilitation; it is underestimated compared with other interventions. There is a need for further high quality RCTs investigating the effect of exercise and the role of supervision of exercise in terms of patient’s compliance.
References


25. Gummesson C, Warm MM, Atroshi I. The shortened disabilities of the arm, shoulder and hand questionnaire (quick DASH): validity and reliability based on responses within the full-length DASH. BMC Musculoskeletal Disorders. 2006; 7:44.

musculoskeletal disorders, but ratings are strongly influenced by current status. Journal of Clinical Epidemiology. 2010; 63:760-766.


8 Extended result

This chapter presents the statistical analyses and results, not emphasized or presented in the previous article.

8.1 Characteristics of study population

Before randomization, characteristics of study population were registered. Depict of these characteristics are in table 1 in the article.

8.1.1 Difference between groups

There were a higher proportion of males in the manual therapy group and patients had higher education and worked more frequent in the office, compared to the other groups. Further, the patients in exercise alone group had a higher level of mean pain scores at baseline, compared to the other groups.

8.2 Pain intensity and clinical findings

We explored the distribution of pain intensity (continuous variable) within each group at baseline, before further statistics analysis. There are several ways to explore a continuous variable, and a boxplot is one option. It provides us indication of the variability in scores for within all three groups, and allows a visual inspection of the difference between groups (figure 1). All three groups showed a normal distribution of pain scores, but the exercise alone group had a significantly higher mean of pain intensity and data showed more skewness than the other groups.

8.2.1 Confounding variables

The gathering of data in this study is from all the levels of the factors that are of interest. We have controlled for the cofounding variables by including them in the statistical analysis as co-variates, referred to as fixed effects when using mixed model. Test of fixed effects, as in co-variates and their p-values are depicted in table 1.
Figure 1. Boxplot: a visual inspection of the difference between groups, and check for normality.

Table 1. Test of fixed effects (co-variates)

<table>
<thead>
<tr>
<th>Co-variates</th>
<th>P – value**</th>
<th>P – value **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;0.01</td>
<td>&lt;0.93</td>
</tr>
<tr>
<td>Gender</td>
<td>&lt;0.03</td>
<td>&lt;0.76</td>
</tr>
<tr>
<td>Level of education</td>
<td>&lt;0.00</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Outcomes</td>
<td>&lt;0.00</td>
<td>&lt;0.33</td>
</tr>
<tr>
<td>Time</td>
<td>&lt;0.00</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

** All measurements considered

Fixed effects for primary outcome

Co-variates as age, gender, level of education and time were significant at the .05 level. This means that age, gender, level of education and time are potentially important predictors of the
dependent variable (pain relief). Therefore, was it logical to explore the mean pain scores in each group, in order to compare it to the other groups. These estimates of adjusted means are depicted in **Table 2**, and are the basis for further analysis.

**Fixed effects for secondary outcomes**

Co-variates as level of education and time were significant at the .05 level. This means that level of education and time are potentially important predictors of the second dependent variable (functional capacity of elbow and arm).

**Table 2. Adjusted mean pain group wise**

<table>
<thead>
<tr>
<th>Groups of intervention</th>
<th>Mean*</th>
<th>Mean**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise alone</td>
<td>4.8</td>
<td>4.03</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>3.9</td>
<td>2.82</td>
</tr>
<tr>
<td>Manual therapy</td>
<td>4.1</td>
<td>3.37</td>
</tr>
</tbody>
</table>

* Unadjusted mean pain  
** Adjusted mean pain for multiple co-variates

**8.3 Outcomes and estimations**

**8.3.1 Primary outcome**

The difference in mean pain score between baseline and last measurement were significant (p<0.001), the estimated mean score of pain relief for the study sample with 95 % CI was 1.83 [-2.54; -1.12]. The acupuncture and manual therapy group showed a gradual and very similar pattern of pain relief, while exercise alone showed less improvement. Patients in exercise alone, had higher levels of pain than treatment groups, the estimated mean score of pain for exercise alone (all measurements considered) with 95 % CI was 4.03 [3.56; 4.51], and 2.82 [2.46; 3.18] for acupuncture and 3.37 [2.88; 3.86] for manual therapy group. Pairwise comparisons (groups) of mean difference in pain relief (all measurements considered) are depicted in **Table 2** in article.
8.3.2 Gender difference

In addition to pain relief, a gender difference emerged when we explored the data. Females had significantly higher levels of mean pain than males (p=0.02), more dominantly in the exercise alone, compared to the other groups, the estimated mean pain for females (all measurements considered) with 95 % CI was 3.67 [3.25; 4.09] and 3.15 [2.80; 3.49] for males. The estimated differences between gender and groups are depicted in figure 3.

![Figure 3](image.png)

**Fig. 3** Adjusted mean scores of pain intensity from baseline to last follow-up, compared by groups and gender.

8.3.3 Secondary outcomes

The difference in mean functional capacity of elbow and arm between baseline and last measurement were significant (p<0.001), the estimated mean score of functional capacity of elbow and arm for the study sample with 95 % CI was 12.20 [5.40; 19.00]. The acupuncture and manual therapy group showed a gradual and very similar pattern of improved function, while exercise alone showed less improvement compared to the other two groups. Patients in exercise alone had higher levels of disability of elbow and arm than those in the treatment groups, the estimated mean score of functional capacity of elbow and arm for exercise alone (all measurements considered) with 95 % CI was 32.31 [25.94; 38.69] and 27.40 [22.48; 32.33] for acupuncture and 27.35 [20.61; 34.09] for manual therapy.
Overall, all measurement considered, all participants have improved their elbow and arm function over time; however, our data did not reveal any between-group differences. The presentation of pairwise comparisons (groups) of mean difference in functional disability is in table 3.

Regarding functional disability there were no significant gender difference. Females had higher levels of functional disability than males, but not significant, the estimated mean functional capacity of elbow and arm for females (all measurements considered) with 95 % CI was 29.52 [23.71; 35.33] and 28.54 [23.81; 33.26] for males.

Table 3. Pairwise comparisons (groups) of mean difference in functional disability, all measurements considered.

<table>
<thead>
<tr>
<th>Pairwise comparisons of groups</th>
<th>Mean difference*</th>
<th>SD</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manual therapy compared with acupuncture</td>
<td>0.05</td>
<td>3.72</td>
<td>0.99</td>
</tr>
<tr>
<td>Exercise alone compared with acupuncture</td>
<td>4.91</td>
<td>3.16</td>
<td>0.18</td>
</tr>
<tr>
<td>Exercise alone compared with manual therapy</td>
<td>4.96</td>
<td>4.03</td>
<td>0.22</td>
</tr>
</tbody>
</table>

* Quick-DASH (0-100). A higher score indicates a greater disability.
** Adjusted for multiple comparisons.
9 Discussion

The discussion in this chapter will focus on both methodological aspects as well as the extended result, as in clinical implications. Initially, this is an examination of potential strengths and bias concerning the study population, inclusion and exclusions criteria, study design, methods for data collection and statistical methods. Then, there is a discussion of extended results in relation to existing evidence and clinical reasoning.

9.1 Methodological aspects

9.1.1 Study population
In terms of restricted time and capacity, our study population was restricted to only one medical center in Oslo (NIMI). NIMI is a private medical center, specialized in sports medicine and rehabilitation of musculoskeletal conditions. Therefore, our result may not be representative for the general population in Oslo, or other places in Norway. In a full-scale trial, it would be necessary to widen our search for candidates with LE.

9.1.2 Inclusion and exclusions criteria
We did not differ between the four stages of tendinopathy. If we had been less open in inclusion criteria, and more specific concerning the duration of symptoms and stages of tendinopathy, it might have changed our results. Co-morbidities as neck and shoulder pain was selected as an exclusion criteria since those patients are reported to have a poorer prognosis in regard to durations of symptoms of LE and outcomes of treatment.

9.1.3 Study design
We were interested in exploring the clinical effectiveness of several physical treatments, applied in a combination and compared to a common control group (active). The idea was that the combination of physical treatments is complimentary, and we were interested in assessing their interaction as well as comparing the between-groups effectiveness. A multi-arm study compares several experimental treatments against a common control group. An advantage of such a design over separate two-arm studies is that a single control group is used. In addition to that, such studies allow for fair comparison of different experimental treatments, because you make the comparisons against the same control group and under a single protocol, so that relevant features of the study, such as clinical setting, inclusion and exclusion criteria, are the
same\textsuperscript{35}. For most diseases, as with LE, there are multiple new treatments at the same stage of clinical development, but very few physical treatments have shown consistent effectiveness over other\textsuperscript{11}. Therefore, there is a need for alternative trial designs to maximize the number of treatments, tested in one single trial.

Under ideal study circumstances, there would be a fourth arm in the study design, a control group, where the patients do not perform any exercises, nor receive any additional treatment. With a untreated control group, we would also be able to investigate the clinical effectiveness of exercise alone. Because of pragmatic reasons, we chose not to. Our decision was based upon ethical reasons and previous research. The effectiveness of exercise is well established, and is considered the cornerstone in rehabilitation of tendinopathy. Furthermore, it did not seem ethical to let patients just wait and see, instead of receiving usual care, from a clinical point of view.

9.1.4 Efficacy versus effectiveness

We can characterize a RCT as an \emph{effectiveness} or \emph{efficacy} trial. The term efficacy reflects on an ideal setting, where the testing of research hypothesis is under ideal study circumstances. Effectiveness refers to a pragmatic trial, seeking answers to whether an intervention will work under usual conditions\textsuperscript{52}. Our primary objective of the present pilot study was to investigate the clinical importance of acupuncture and manual therapy treatment of LE, in addition to eccentric exercise. The project was ambitious, with several treatment modalities in a clinical setting, where you can’t possibly control for all confounding variables, so therefore a more pragmatic trial was conducted. With access to patients in a clinical setting at NIMI, it was more natural and practical to explore the effectiveness, rather than the efficacy of treatment of LE. We also believe that the term effectiveness reflects the purpose of the pilot on which this thesis is based upon.

9.1.5 Methods of data collection

The patients reported their pain intensity and other symptoms electronically, with pre-made standardized forms (PROMs). This way of data collection makes it possible to have several measurements and follow-ups. On the other hand, would objective assessment as pain-free grip test, measured with dynamometer, possibly further elucidated our findings. Hence, further research as in a full-scale trial, is required to determine if the treatments are effective, when using measurements that are objective, in addition to PROMs.
9.1.6 Statistical method

Pre-study calculation is important\textsuperscript{48}. Hence, we provided a priori estimate of sample size, before commencing the study, although the present study was planned as a pilot for a hopefully future full-scale study. Our choice of statistical method was a linear Mixed Model for repeated measurements. This model is containing both fixed and random effects, which is very useful in social sciences, using primary data generated in the clinical environment\textsuperscript{53}. Particularly useful in settings, where repeated measurements are made on the same statistical units, as with our repeated measurements of pain and disability. Because of their advantage in dealing with missing values, mixed effects models are often preferred over other more traditional approaches such as ANOVA\textsuperscript{53}.

When observing a difference in outcome (pain relief) between groups, you need to consider whether the effectiveness is truly because of exposure (treatment) or if an alternative explanation is possible\textsuperscript{54}. This is also known as confounding variables, which can adversely affect the relation between exposure and outcome. In a clinical trial, this can happen when the distribution of a known prognostic factor differs between groups being compared. The results may show a false correlation between the exposure of treatment and outcome (pain relief), leading to an incorrect rejection of the null hypothesis\textsuperscript{54-55}. Hence, we explored the distribution of known prognostic factors in-between groups. Because of a small study population, with a tendency to differ in prognostic factors between groups, being compared, we controlled for confounding variables by including them in the statistical analysis, a mixed model.

9.2 Evidence-informed clinical reasoning

It’s proposed in the literature, when consulting a patient with LE, that the clinicians should base their recommendations for treatment on the presented characteristic, which are known to be associated with the risk of a good or poor prognosis. Such as tendon pathology, presence of co-morbidities, work related factors and severity of pain and disability at baseline\textsuperscript{6}.

9.2.1 Tendon pathology

As outlined under pathophysiology, it is a continuum of tendon changes in patients with LE. The last stages of tendinopathy has poorer prognosis\textsuperscript{8}, and it is discussed that rehabilitation of LE should differ based upon the stages of tendinopathy\textsuperscript{8, 18}. We included patients with symptoms duration for two weeks, and longer. If we had distinguished between acute and
chronic stages of tendinopathy, we could have adjusted for the difference in duration of symptoms in the statistical analysis, because duration of symptoms, as in different stages of tendinopathy, might affect the outcome.

Another example is that a former study has found that the presence of an intra substance tendon tear detected by US, was significantly associated with poorer prognosis for the patients with LE\textsuperscript{6}, and indicated greater likelihood of failing physiotherapy management, including an eccentric exercise program\textsuperscript{20}.

A clinical experience from treating patients at NIMI is, that those patients with intra substance tendon tear confirmed with imaging (MRI or US), get more pain from load and exercise than those who don’t have an injured tendon. Hence, make the rehabilitation of LE more difficult. Therefore, should those patients manage their condition differently from those with absence of tears in tendon? Because we did not have imaging (MRI or US), as an inclusion criteria in this pilot study, we do not know if any of our patients did have injury to their tendon, which possibly affected the result of treatment and/or exercise. Based upon clinical experience, I would argue that there is a need for further investigation of those issues in the managing and rehabilitation of LE.

9.2.2 Severity of pain at baseline

LE may present as a continuum of symptoms, ranging from mild to severe pain, and disability. There is strong evidence that patients with greater baseline pain and disability have a poorer long-term prognosis, and it appears to modify the effects of physiotherapy treatment in short-term\textsuperscript{18-19}.

Group of exercise alone had higher levels of pain at baseline, compared to treatments groups. Those with high levels of pain at baseline have shown greater potential to score better after treatment. Exercise alone did not have this potential; they score worse than the other groups, which had lower pain score at baseline. Based upon the results of the present pilot study, we could argue that, as a clinician, we may need to focus initially more on pain relieving techniques or modalities in addition to exercise. For those with severe pain at baseline, the approach should maybe be more in line with management of persistent chronic pain, possibly involving pain education and several treatments sessions, compared to those with lower levels of pain. In conclusion, there is no size that fits all, in the managing LE.
9.2.3 Gender differences
In our explorative result, there was a gender difference emerging. Females had significant higher levels of mean pain score than males, all measurements considered. From a clinical point of view, females with chronic pain conditions tend to report a higher pain intensity than males, but former research on LE can’t confirm a gender difference. It is of interest, that the gender differences were more dominantly in-group of exercise alone, where the participants did not receive additional physical treatment for pain relief, nor interacted with a therapist after enrollment in the study. Based upon this result, it could be of interest to investigate a possible gender difference, and if it is associated with the risk of a good or poor prognosis, in the managing of LE.

9.3 Exercise being the cornerstone of rehabilitation of tendinopathy
The effect of exercise training on stimulating tendon, remodeling and production of muscular adaptive responses, seems to be documented. In addition, exercise may have local analgesic effect on patients with LE. The choice of eccentric versus concentric exercise was based upon research and clinical experience at NIMI, where we have managed LE with exercise programs, including eccentric exercise, for several years. A key concept in the use of eccentric exercise in clinic, is the effects of this type of muscle action on the patient’s perceived exertion. Further, the outcomes of strength exercise programs seems to depend on the patient’s compliance, with continued exercise and motivational levels, which are sufficient for intense efforts.

We did not supervise the patients, when performing their exercise program, in this present pilot. In an optimal clinical and trial setting, we would prefer to supervise the exercise performance, in order to allow for an optimal progression of load management. Based upon experience with strength exercise for tendinopathy, the progression of load need to be slow, and performed below the patient’s pain threshold. To our knowledge, there is no research, exploring the role that supervision of exercise has to play in terms of patient’s compliance.
9.4 Statistical significance versus clinical importance

Authors of RCTs usually report statistically significant difference between groups, and base their conclusion on this statistical significance. The P value is not very informative, because it only indicates the chances of the observed effect, and do not consider its size. Meaning, that the P value does not indicate if the effect is clinically important. Therefore, reports based upon statistical significance rather than on clinical importance, may be too positive in some occasions\textsuperscript{51, 59}.

The effectiveness of treatment, needs to be meaningful for the patient, which is a positive effect on how the patients feel (pain) and how they function\textsuperscript{41}. Based on former publications, we expect the MIC in pain, to be a reduction of two point on NRS, which is to be associated with the concept of much better improvement in one treatment group compared to another. Two point differences between groups on NRS was also the basis of our power calculations.

The result of the explorative statistical analysis was, that patients receiving treatment in addition to eccentric exercise, either acupuncture or manual therapy experienced a better pain relief than those receiving eccentric exercise alone. The difference was of statistical significance, and highly so (p<0.01), between acupuncture and exercise alone with a mean pain change score of 1.21 (0.27). There is to our knowledge, however, no clear definition of the size of in-between group differences, and when they should be viewed as clinical significant different, meaning that one treatment is clinically better than the other(s). The explorative analysis also shoved some differences in pain relief between acupuncture and manual therapy, but the differences were even smaller and of unsure clinical value. Narrow confidence intervals may explain statistically significant differences between groups despite debatable clinically sizes. Reviews on physical therapy, including exercise program, for the treatment of LE found that the difference between treatment and control groups were larger than differences between treatment\textsuperscript{57}. This means that the difference between different treatment modalities seems to be lower than the difference between treatment and their respective control groups, as with our result.

These results are from a small study population (a pilot), with much, less power than calculated for a full-scale trial, and with clinically changes from baseline to end of study just under the pre-specified magnitude and differences in pain and disability scores between treatment groups.
of unsure clinical significance. Therefore, we must conclude with caution. The overall effect of treatment is however statistically significant and near to clinically significant, therefore, it would be of worth to follow up the present pilot study in a subsequent larger study.

9.5 Clinical implications and further research

A significant gap in the current literature, an area of growing interest, is the effect of potentially confounding variables on treatment outcomes. Certain clinical characteristic and/or underlying pathophysiological characteristics may modify treatment effects.

The role of exercise in managing LE across the severity spectrum should be clarified, including optimal dosage and type of exercise for people with mild, moderate or severe symptoms of LE. Given the exercise is considered the cornerstone of rehabilitation; it is understudied compared with and in combination with other interventions. There is a need for further well-controlled RCTs investigating the effectiveness of exercise and the role that supervision of exercise has to play in terms of patient’s compliance.

The effectiveness of alternative pain relief such as acupuncture for people with LE, is worthy of further investigation.

10 Conclusion

Patients receiving treatment in addition to eccentric exercise, either acupuncture or manual therapy experienced a better pain relief than those receiving eccentric exercise alone, during treatment and up-to 12-week follow-up. In addition, in explorative analysis a gender difference emerged; females had higher levels of pain than males, more dominantly, in-group of exercise alone.

Explorative analysis shoved some differences in pain relief between acupuncture and manual therapy, but the differences were of debatable clinical value.

This pilot study indicate that the methods and procedures are feasible, and the results of the pilot is worth following up in a subsequent larger study.
11 References

25. Lorentz D, Reiman M. Clinical Commentary. The role and implementation of eccentric training in athletic rehabilitation: tendinopathy, hamstring strains, and ACL reconstruction.


44. Gummesson C, Warm MM, Atroshi I. The shortened disabilities of the arm, shoulder and hand questionnaire (quick DASH): validity and reliability based on responses within the full-length DASH. BMC Musculoskeletal Disorders. 2006:7-44.


12 Appendix

Overview of appendixes

Appendix 1 The regional Committees for Medical Research Ethics (REK) 1.

Appendix 2 The regional Committees for Medical Research Ethics (REK) 2.

Appendix 3 The Norwegian Centre for research Data (NSD)

Appendix 4 The written consent-form

Appendix 5 Eccentric exercise program
Appendix 1

Kjersti Stordein
Universitetet i Oslo

2014/1520 Fysioterapi og skapspunkt ved tezimalbe

Forskningsansvarlig: Universitetet i Oslo
Projektføder: Kjersti Stordein

Vi viser til rekord om forblekkspunktning av utsøvende forskningsprosjekt. Tekstaden ble behandlet av Regional komité for medicinsk og helserelevant forskningsetikk (REK) ved et møte 17.09.2014. Verdesignering av gjort ved hjemmel i forsknings etikkloven (fet) § 16, jf. forsknings etikkloven § 4.

Projektføder: Dette er

Terminalitis er en alvorlig problemer for både individ og samfunnet, med en prevalanse på 1-2 % i den norske befolkningen. Hvis smerter kan tilstående vara fra et halvt til to år i gjennomsnitt, og det er assosiert med et sykemønster på 3 % av arbeidstakerne med terminalitis. Formålet med denne studien er å sammenligne den kliniske effekten av manuell terapi med skapspunkter behandle av terminalitis. Dette er viktig grunn vissent smerte for individet, samt kostnader for samfunnet.

Vi har redaksjon av smerte og sykemønster vil være av stor verdi. Studie design er experimentell og prospektiv. Designet er tre-året og randomisert.

Forskningsprosjektet som skal beskrives er manuell terapi eller skapspunktter er en effektiv behandlingsform i henhold til smerte i forsterkning for patienter med terminalitis. Sekundære utviklinger er funksjon, livshell og sykemønster.

Kommisjonen vedrørende

Kommissionen har ingen forskningsmønster innvendige til at prosjektet gjenomføres.

Delegasjonen ansvarlig for til 3 til å megge. Denne meggeenhetens ikke behandling i forskningsperioden som går over 12 åtar. Prosjektføder skriver i tilfellen at man mener dette er forvarlig da man ikke har klarer retningslinjer for behandling av terminalitis og at mange patienter ikke mener slik behandling ved terminalitis. Kommissionen fastsetter at tonet av det som klart enklere og manolvering av skapspunkt.

Vedtektskommissionen godkjenner prosjektet i henhold til forsknings etikkloven § 1 og § 23

Godkjenninga er gitt under forutsetning av at prosjektet gjenomføres slik det er beskrevet i teksten.

Til Kjersti Sørheim

2014/1530 Pynoterapi og skjønnhet ved termalbevegelse

Forskningsutvalg, Universitetet i Oslo
Prosjeksleder Kjersti Sørheim


De omtalte endringene er bedraktet i stikkmetro for projektnøkkel og foreslår selv om de nåter forordningens samfunnsforbeholder fra 45 til 55. I tillegg se det gjenskriver endringen i aksjeselskap- og skattekomitéutviklingen for å bedre prosessforbedringen og fremme generalforsamlingsbevirkningen.

Kommenses vedtak
Komisjon har aner innenfor til de omtalte endringene.

Vedtek
Komisjon har vedtatt endringen og godkjent prosjektet slik det er foreslått med hensyn til betjeningsforbedringen § 11.

Godkjenningene er gitt under forutsetning av at prosjektet godkjenner slik det er beskrevet i endringen.

Klagegebyr
Dekk klage på komisjonen vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til RBK nr.-sett.
Klippenes avtale for de omtatte bestemt. Dersom vedtak oppfyller av RBK nr.-sett, sender klagen ved inviter til Den nasjonale forkningsstays komité for medicin og helsefor endelig vurdering.

Vennligst oppgi vist referansenummer i korrespondansen.

Med vennlig hilsen

Kari W. Rusten
avdelingsleder
Appendix 3

Kersti Seelheim
Institutt for helset og samfunn
Universitetet i Oslo
Pax 1069 Blindern
0317 Oslo

AVSLUTTET SAKSBEHANDLING

Personvernombudet for Tanksing viser til meddelelsen med tiden 11.12.14 for prosjektet:

69159
Clinical comparative effect of 30 minutes music acupuncture treatment of internal
psychosis.

Personvernombudet tar til oppmøtet av prosjektet er medlem av Regional komité for medisinsk og
helbredende forskningstilfelle (REK), som opplyst i saksdekkets punkt 12. Personvernombudet legger
dette til grunn og avslutter dermed saksbehandlingen av meldingen uten redskabelig behandling. Vi
avslutter all oppfølging av prosjektet.

Til gjerne kontakten dersom noe er uklart.

Veiledig bidrager

Kersti Hungstvold

Kontaktperson: kersti.hungstvold@nsd.uib.no

Kap. Institutt for helset og samfunn
Kersti Bostad
Appendix 4

Forespørsel om deltakelse i masterstudentprosjektet:
”Fysioterapi eller akupunktur behandling av tennisalbue”

Prosjektleder: Kjersti Storheim
Masterstudent: Katrine Bostrøm

Bakgrunn og hensikt
Du forespørs med dette for å delta i en studie hvor vi undersøker om behandling med fysioterapi eller akupunktur kan redusere smerte i albue- og underarmsmuskulatur, også kalt tennisalbue.

Tennisalbue er et økende problem for både individet og samfunnet, med en prevalens på 1-3 % i den norske befolkningen. Denne tilstanden rammer både kvinner og menn, og oppstår som oftest i forbindelse med tungt og/eller repeterende arbeidsbelastninger av sene- og underarmsmuskulatur.

Prosjektet er et masterprosjekt ved Universitetet i Oslo (UiO), avdeling for helsefag, og er et samarbeid mellom leger, fysioterapeuter og akupunktører ved Norsk Idrettsmedisinsk Institutt (NIMI) og UiO. Formålet med masterprosjektet er å undersøke om behandling i form av akupunktur eller fysioterapi kan redusere smerte og bedre funksjon hos pasienter med tennisalbue. For og delta skal du ikke ha fått kortison injeksjon for tennisalbue de siste 4 ukere.

I alt 36 antall pasienter skal delta i studien og resultatene forventes å være klare våren 2016.

Hva innebærer studien?

Gruppe A
Du vil få inntil 8 fysioterapi behandlinger spredt over 4 uker.
Behandlingene vil foregå på NIMI og utføres av en erfaren manuell terapeut.
Du vil også få instruksjoner i hvordan du skal gjennomføre et enkelt hjemme treningsprogram for tennisalbue daglig, som vil ta 5 min. å gjennomføre.

Gruppe B
Du vil få inntil 8 akupunktur behandlinger spredt over 4 uker.
Behandlingene vil foregå her på NIMI av en erfaren akupunktør.
Du vil også få instruksjoner i hvordan du skal gjennomføre et enkelt hjemme
treningsprogram for tennisalbue daglig, som vil ta 5 min. å gjennomføre.

**Gruppe C**
Du skal leve som normalt i 12 uker, og mottar ingen aktiv behandling. Du vil få instruksjoner
i hvordan du skal gjennomføre et enkelt hjemme treningsprogram for tennisalbue daglig, som
vil ta 5 min. å gjennomføre.

**Mulige fordeler och ulemper**
Mulige fordeler kan være redusert smerte i albue- og underarmsmuskulatur, og dermed økt
funksjon og arbeidskapasitet. Det er rapportert få bivirkninger med akupunktur behandling.
De vanligste bivirkningene er smerte fra nålen, samt lette blåmerker fra der nålen satt. Det er
ikke rapportert bivirkninger fra fysioterapi behandling av tennisalbue.

**Hva skjer med informasjonen om deg?**
Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med
studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte
gjenkjenningende opplysninger. En kode knytter deg til dine opplysninger gjennom en
navneliste.

Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som
kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når
disse publiseres.

**Frivillig deltakelse**
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt
samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling.
Dersom du ønsker å delta, undertegner du samtykkeerklæringen her under. Om du nå sier ja
til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige
behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du
kontakte:

Katrine Bostrøm på mobil 472 96 551 / katrine.bostrom@nimi.no og veileder ved UiO,
 førsteamanuensis Kjersti Storheim, telefon 22 11 77 40 / kjersti.storheim@medisin.uio.no.

**Samtykke til deltakelse i studien**
Jeg er villig til å delta i studien

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(Signert av deltaker, dato)

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(Signert av inkluderende lege, dato)
Laterale albuesmerter
Treningsprogram for sene- og muskelproblematikk

Nimi – Norsk idrettsmedisinsk institutt
Postadresse: P.b. 3843, Ullevaal Stadion, 0805 Oslo
Besøksadresse: Sognsveien 75 D
Kundesenter: 02430
E-mail: post@nimi.no
www.nimi.no
Treningsprogrammet

- Du skal trene i 12 uker.
- Du skal trene 1 gang om dagen i alle ukedagene.
- Det er OK med smerte UNDER øvelsene, men ikke tiltagende smerter dagen etter.
- Etter som smerten avtar skal belastningen økes med mer VEKT (vannflaske).
- Alle aktiviteter (utenom øvelsene) som resulterer i SMERTE, bør unngås i opptreningsperioden.

Beskrivelse av treningsprogrammet

Du fyller en vannflaske med vann. Startvolumet for kvinner er en halv liter, for menn en liter. Kvinner skal øke treningsvolumet med en halv desiliter, og menn skal øke med en desiliter, når smerten avtar eller en gang i uken.


Figur 1. Utgangsposisjon for øvelsene
