Physiotherapy Department

University of West Attica

Clinical Research Protocol

The effects of low load resistance training with blood flow restriction (BFR) in patients with lateral elbow tendinopathy: a randomized controlled trial

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BACKGROUND

Lateral elbow tendinopathy (LET), also widely known as “tennis elbow”, is the most common musculoskeletal disorder of the elbow causing a significant functional decline with increased disability and productivity loss (1-3). The prevalence of LET ranges from 1% to 3% (4, 5), and it is strongly associated with repetitive activities, office occupation, older age, female gender, smoking, shoulder tendinopathy and obesity (6-8). The common diagnostic factor is pain over the lateral humeral epicondyle during palpation and gripping that may radiate distally into the forearm (9). Although the clinical presentation of LET has been well documented, the aetiology remains inconclusive and the underlying pathophysiology is complex (10, 11).

The conservative management is considered to be the first line of treatment with exercise, orthoses, manual therapy, physical therapy modalities, acupuncture and multimodal physiotherapy treatment (9). However, evidence supporting a form of the most effective treatment approach is unclear. Exercise including eccentric, isometric or concentric-eccentric appears to be the most popular treatment approach with or without passive interventions modalities or injections (12, 13). A number of systematic reviews underlined the value of eccentric exercise in the management of LET at short-term follow-up, however, their superiority compared to other active interventions remains inconclusive (11, 14, 15). The effectiveness of traditional training programmes in the management of LET is unclear since only a few studies report their exercise program in ample detail to allow full replication in clinical practice (Bisset et al., 2006; Coombes et al., 2013; Vuvan et al., 2020)

Important exercise properties such as load, dosage, time under tension, rest periods, acceptable pain level, equipment, duration, frequency etc. are critical barriers to provide clinical recommendations for the optimal exercise selection in LET. Evidently, the research evaluation of innovative and well-developed active interventions seems essential to improve evidence-informed clinical practice in the current field.

STUDY RATIONALE

During the last few decades, a new type of training using Blood Flow Restriction (BFR) has been suggested as an effective way to increase muscle strength and mass both in healthy and unhealthy individuals (Patterson et al., 2019). Exercise programmes using heavy loads such as 60- 70% of one repetition maximum (1RM) were considered essential to elicit muscle hypertrophy and strength in 6-8 weeks' time (16)However, low load resistance training using 20%–30% 1RM with BFR, has shown significant improvements in power and hypertrophy of skeletal muscles compared to non-BFR load-matched controls. BFR training has its origins on 'Kaatsu training' and uses a pneumatic tourniquet system which applies an external pressure, to the most proximal region of the upper or lower limbs (17). The use of the tourniquet system results in a partial restriction of arterial blood flow to structures distal to the cuff, while the venous return is also substantially blocked (17, 18). Key role in skeletal muscle reaction to BFR training is thought to be the inadequate oxygen supply (hypoxia) (19, 20).

The positive clinical use of BFR training has been well documented in systematic reviews including a range of musculoskeletal conditions such as knee

osteoarthritis, anterior cruciate ligament injury, Achilles tendon ruptures, patella tendinopathy etc. (21, 22). The use of BFR in clinical conditions has given promising results not only for muscle strength and mass but also in pain reduction (18, 21, 23, 24). The use of low load resistance training with BFR in conditions where the presence of pain limits the use of high load resistance exercises can be extremely valuable (25, 26). A study including patients with patellofemoral pain syndrome reported that BFR training had statistically better results compared to non BFR programmes in pain reduction and disability scores even with substantial lower load of exercises at 8 weeks follow-up (23). In the same line, the study by Korakakis et al., (2018) including patients with anterior knee pain showed significantly better results of a low load resistance training BFR programme compared to a non-BFR programme in pain reduction lasting for at least 45-min post- intervention. Similarly, studies including patients with anterior cruciate ligament repair showed that the addition of BFR training was more effective compared to the traditional rehabilitation in muscle changes and pain reduction as well (21, 27). According to the authors knowledge there are no research investigations for the effectiveness of BFR training in upper limb tendinopathies including LET. The use of an optimal exercise programme in patients with LET remains inconclusive and the investigation of this new type of rehabilitation training could be valuable in improving the clinical effectiveness of active treatments.

STUDY OBJECTIVES

To evaluate the effectiveness of low load resistance exercises with blood flow restriction in increasing strength, reducing pain and improving function compared to usual exercises in patients with lateral elbow tendinopathy.

STUDY DESIGN

Sample

Forty-two patients, men and women, 18-50 years old with LET and symptoms for more than 2 weeks. Inclusion criteria: pain provoked by palpation on the lateral epicondyle, Cohen's test, Maudsley test, Mill's test, pain free grip strength. All participants will sign an informed consent form prior their participation to the study. Study approval will be obtained from the Ethics Committee of the University of West Attica. Exclusion criteria: shoulder tendinopathy, cervical radiculopathy, reumatoid arthritis, neurological deficit, radial nerve entrapment, past treatment for the elbow before entering the study, professional athletes, LET of the same side in the last 3 years, serious cardiovascular diseases, venous deficiency, history of heart surgery, cancer history, breast surgery, orthopaedic surgeries during the last 6 months, thrombosis, body mass Index ≥ 30, Crohn syndrome, family or personal history of pulmonary embolism

Procedure

Potential participants will be recruited through public invitations in the University of West Attica, local hospitals, General Practitioners and Orthopaedic surgeons.

Individuals who will respond are going to be examined by a musculoskeletal specialist physiotherapist.

Measurements

The primary outcome measures include self-perceived recovery measured using 6-point Global Rating of Change (GROC) pain free grip strength pain (PFGS) and functionality. GROC measurement will contain a six point Likert scale describing the change from much worse to totally improved, PFGS will be measured with a Jamar hand dynamometer, pain with 0-10 scale (Numerical rated pain scale) and functional disability with the patient-rated tennis elbow (PRTEE) questionnaire. Secondary outcomes include: Tendon thickness, neovascularity, presence of spurs, calcification and/or tears in the common extensor tendon (lateral epicondyle) measured with diagnostic ultrasound imaging. Also, isometric strength measurements of elbow flexors and extensors will be included using the BioFet force evaluation system (mean of three efforts of the maximum isometric contraction). All measurements will be taken at baseline, 6- and 12-weeks follow-up.

Interventions

Participants will be randomized with an appropriate software to either a blood flow restriction exercise programme or a placebo blood flow restriction exercise programme. A concealed allocation will be applied. Assessor, therapists and patients will be blinded. Both groups of patients will be treated with a usual exercise programme in lateral elbow tendinopathy (28). One group will use blood flow restriction and the other group placebo blood flow restriction (cuffs without air

inflated). The exercise programmes will be held in physiotherapy sessions (twice a week) for 6 weeks. Also, all patients will be treated with soft tissue massage, the same appropriate advice and a home exercise programme (written workbook). All patients will fill in a diary for monitoring adherence and co-interventions.

STATISTICAL ANALYSIS PLAN (SAP)

Demographic and Baseline Characteristics

All randomized participants will be included in statistical analysis. The following demographic and baseline characteristics will be summarized and statistically analyzed: gender, age, height and weight, smoking habits, type of work, physical activity level, previous episodes of LET, time course of condition, severity of pain, disability scores (PRTEE), pain free grip strength, isometric strength test of elbow flexors and extensors.

Sample Size and Randomization

The primary outcome measure for the power calculation is the difference between study groups in the change of PFGS between baseline and 12 weeks follow-up. The MCID of PFGS has been evaluated in a group of patients with LET with an age of 42±9 years and relatively equal distribution of males and females (29). These researchers found PFGS to better discriminate improved from non-improved patients with a threshold of 7kg showing the greatest accuracy. Also, we used prior effect estimates from an RCT (30), which compared different exercise programmes in patients with LET reporting a standard deviation in PFGS 7.1 kgr. We have set alpha=0.05 and beta=0.80 and resulted in n=16.15 per treatment group (31, 32).

By estimating up to 10% losses to follow-up our sample was set at 36 participants (31, 32). Patients will be randomly allocated into the study groups. The principal investigator will be responsible for the random allocation by using an online random allocation software. Participants, therapists and assessor will be blinded to the allocation into the study groups.

Data Analysis

All randomized study subjects will be analyzed using Intention-to-treat analysis. Moreover, all randomized study subjects completing the trial period (complete cases) will be analyzed using per protocol analysis. For the scope of sensitivity analysis, study subjects with missing data on any of the variables will be excluded from the analysis. Hence, the sensitivity of the results regarding the pattern of missing data will be investigated. Model based multiple imputation will be used for both primary and secondary outcomes.

All outcomes will be presented using descriptive statistics; normally distributed data by the mean and standard deviation (SD) and skewed distributions by the median and interquartile range (IQR). Binary and categorical variables will be presented using counts and percentages. The SPSS software (version 25) will be used for all statistical analysis.

Primary outcomes

The primary analysis will compare the two interventions on their mean change in PFGS, PRTEE scores, pain reduction. The estimated difference in mean change

from baseline to 6 and 12 weeks and the corresponding 95 % confidence interval (CI) will be presented. We will estimate all continuous outcome measures by using baseline values as covariates in linear mixed models. For GROC logistic regression will be used and the odds ratio (OR) including 95 % Confidence Intervals (CI) will be presented.

Secondary Outcomes

As far tendon thickness and isometric strength of elbow flexors and extensors the difference in mean change from baseline to 6 and 12 weeks and the corresponding 95 % confidence interval (CI) will be presented. Tendon neovascularity, presence of spurs, calcification and/or tears in the common extensor tendon (lateral epicondyle) incidence will be analyzed using logistic regression and the OR including 95 % CI will be presented.

SUBJECTS CONFIDENTIALITY AND ETHICAL CONSIDERATIONS

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects. Data will be kept safe using records with coded numbers. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers. Patients will participate voluntarily, will be free to withdraw at any time and, sign a consent form prior entering the study.

References

1. Shiri R, Viikari-Juntura E. Lateral and medial epicondylitis: role of occupational factors. Best practice & research Clinical rheumatology. 2011;25(1):43-57.

2. Silverstein B VE, Kalat J. Use of a prevention index to identifyindustries at high risk for work-related musculoskeletal disorders of the neck,back, and upper extremity in Washington State,1990-1998. Am J Ind Med.2002;41:149–169.

3. Workcover Queensland. Workcover Queensland annual report 2012-2013. Brisbane Qld A.

4. Shiri R V-JE, Varonen H, Heliovaara M. Prevalence and determinants of lateral and medial epicondylitis: a population study. American Journal of Epidemiology; 2006 164(11):1065–74, Shiri EaV-JLameRoofBPRCR.

5. Werner RA, Franzblau A, Gell N, Hartigan A, Ebersole M, Armstrong TJ. Predictors of Persistent Elbow Tendonitis Among Auto Assembly Workers. Journal of Occupational Rehabilitation. 2005;15(3):393-400.

6. Bugajska J, Zołnierczyk-Zreda D, Jędryka-Góral A, Gasik R, Hildt-Ciupińska K, Malińska M, et al. Psychological factors at work and musculoskeletal disorders: a one year prospective study. Rheumatol Int. 2013;33(12):2975-83.

7. Devereux JJ, Vlachonikolis IG, Buckle PW. Epidemiological study to investigate potential interaction between physical and psychosocial factors at work that may increase the risk of symptoms of musculoskeletal disorder of the neck and upper limb. Occup Environ Med. 2002;59(4):269-77.

8. Roquelaure Y, Ha C, Leclerc A, Touranchet A, Sauteron M, Melchior M, et al. Epidemiologic surveillance of upper-extremity musculoskeletal disorders in the working population. Arthritis and rheumatism. 2006;55(5):765-78.

9. Bisset LM, Vicenzino B. Physiotherapy management of lateral epicondylalgia. J Physiother. 2015;61(4):174-81.

10. Coombes BK, Bisset L, Connelly LB, Brooks P, Vicenzino B. Optimising corticosteroid injection for lateral epicondylalgia with the addition of physiotherapy: A protocol for a randomised control trial with placebo comparison. BMC musculoskeletal disorders. 2009.

11. Cullinane FL, Boocock MG, Trevelyan FC. Is eccentric exercise an effective treatment for lateral epicondylitis? A systematic review. Clinical rehabilitation. 2014;28(1):3-19.

12. Bateman M, Titchener AG, Clark DI, Tambe AA. Management of tennis elbow: a survey of UK clinical practice. Shoulder & elbow. 2019;11(3):233-8.

13. Coombes BK, Connelly L, Bisset L, Vicenzino B. Economic evaluation favours physiotherapy but not corticosteroid injection as a first-line intervention for chronic lateral epicondylalgia: evidence from a randomised clinical trial. British journal of sports medicine. 2016;50(22):1400.

14. Ortega-Castillo M, Medina-Porqueres I. Effectiveness of the eccentric exercise therapy in physically active adults with symptomatic shoulder impingement or lateral epicondylar tendinopathy: A systematic review. Journal of science and medicine in sport. 2016;19(6):438-53.

15. Raman J, MacDermid JC, Grewal R. Effectiveness of different methods of resistance exercises in lateral epicondylosis--a systematic review. Journal of hand therapy : official journal of the American Society of Hand Therapists. 2012;25(1):5-25; quiz 6.

16. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Medicine and science in sports and exercise. 2011;43(7):1334-59.

17. Wernbom M, Augustsson J, Raastad T. Ischemic strength training: A low-load alternative to heavy resistance exercise? Scandinavian journal of medicine & science in sports. 2008;18:401-16.

18. Loenneke JP, Abe T, Wilson JM, Thiebaud RS, Fahs CA, Rossow LM, et al. Blood flow restriction: an evidence based progressive model (Review). Acta physiologica Hungarica. 2012;99(3):235-50.

19. Larkin KA, Macneil RG, Dirain M, Sandesara B, Manini TM, Buford TW. Blood flow restriction enhances post-resistance exercise angiogenic gene expression. Medicine and science in sports and exercise. 2012;44(11):2077-83.

20. Manini TM, Clark BC. Blood flow restricted exercise and skeletal muscle health. Exercise and sport sciences reviews. 2009;37(2):78-85.

21. Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: a systematic review and meta-analysis. British journal of sports medicine. 2017;51(13):1003-11.

22. Slysz J, Stultz J, Burr JF. The efficacy of blood flow restricted exercise: A systematic review & meta-analysis. Journal of science and medicine in sport. 2016;19(8):669-75.

23. Giles L, Webster KE, McClelland J, Cook JL. Quadriceps strengthening with and without blood flow restriction in the treatment of patellofemoral pain: a double-blind randomised trial. British journal of sports medicine. 2017;51(23):1688-94.

24. Korakakis V, Whiteley R, Giakas G. Low load resistance training with blood flow restriction decreases anterior knee pain more than resistance training alone. A pilot randomised controlled trial. Physical therapy in sport : official journal of the Association of Chartered Physiotherapists in Sports Medicine. 2018;34:121-8.

25. Herrington L, Al-Sherhi A. A controlled trial of weight-bearing versus non-weight-bearing exercises for patellofemoral pain. The Journal of orthopaedic and sports physical therapy. 2007;37(4):155-60.

26. Hughes L, Patterson SD. Low intensity blood flow restriction exercise: Rationale for a hypoalgesia effect. Medical hypotheses. 2019;132:109370.

27. Ladlow P, Coppack RJ, Dharm-Datta S, Conway D, Sellon E, Patterson SD, et al. Low-Load Resistance Training With Blood Flow Restriction Improves Clinical Outcomes in Musculoskeletal Rehabilitation: A Single-Blind Randomized Controlled Trial. Front Physiol. 2018;9:1269.

28. Vicenzino B. Masterclass: Lateral epicondylalgia: a musculoskeletal physiotherapy perspective. Manual Therapy. 2003;8:66-79.

29. Stratford P, Gill C, Westaway M, Binkley J. Assessing Disability and Change on Individual Patients: A Report of a Patient Specific Measure. Physiotherapy Canada. 1995;47(4):258-63.

30. Martinez-Silvestrini JA, Newcomer KL, Gay RE, Schaefer MP, Kortebein P, Arendt KW. Scientific/Clinical Article: Chronic Lateral Epicondylitis: Comparative Effectiveness of a Home Exercise Program Including Stretching Alone versus Stretching Supplemented with Eccentric or Concentric Strengthening. Journal of Hand Therapy. 2005;18:411-20.

31. Bland JM. The tyranny of power: is there a better way to calculate sample size? BMJ. 2009;339:b3985.

32. Bland M. An Introduction To Medical Statistics. 2000;13.