TITLE:

Effects of ecoguided percutaneous peroneal nerve percutaneous neuromodulation (EPNM) and neuromuscular exercise in the management of chronic ankle instability (CAI): a randomised clinical trial (RCT).

DATE: 19/05/2023

RESEARCH PLAN:

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INTRODUCTION:

Lateral ankle complex sprain is the most prevalent musculoskeletal injury in the general and athletic population and is associated with long-term pain, disability and high health care costs (1,2). A review of ankle injuries in 70 sports analysed established that lateral ankle sprains accounted for 77% of all injuries (3) where the highest incidence rates were found in sports characterised by running, changes of direction or jumping such as basketball, football or volleyball. (4)

One of the complications of lateral ankle sprain is the development of chronic ankle instability (CAI) characterised by repeated episodes or perceptions of ankle instability, persistent symptoms such as pain, swelling and decreased function with limitations in activities of daily living and sports participation that persist more than one year after the initial injury (4,5). In terms of presentation, different contributing factors have been identified such as mechanical and/or functional impairments. The most common mechanical impairments are: joint laxity, altered kinematics and degenerative or synovial changes in the cartilage of the talocrural joint, while at the functional level they are: deficits in proprioception, muscle strength and balance or dynamic control (6).

In a recent review by Lin et al. the prevalence of CAI in a population with a history of ankle sprain was 46%, with a range between 9 and 76% (7). The wide range is influenced by multiple factors such as gender, age, sporting activity, non-use of external supports, high body mass index or increased talar curvature (7,8). Another study estimated that 50-70% of ankle sprains will develop chronic instability, with a prevalence in the general population of 1.1% in men and 0.7% in women (9) and as high as 23% in the athletic population (10).

As for the symptoms presented by patients with CAI, pain is one of the most frequent, constituting a disturbance in the somatic sphere and a potentially negative factor for the person's functional activity. In a recent review, 55% of patients with CAI had pain, with

differences being found depending on the methodology used for assessment, being up to 59% in the case of the use of quantitative assessments or self-reports and decreasing to 49% by assessing pain through provocation with orthopaedic tests such as stress varus or direct palpation (11).

Another symptom found in patients with chronic instability is a deficit in muscle strength. In this respect, the peroneus longus and peroneus brevis muscles are important stabilisers of the external ankle area and there are studies that show a deficit in the strength of this musculature both in the neutral position and in the maximum plantar flexion position in patients with CAI (12). Another study in university athletes observed a decrease in the strength of the eversor muscles and plantar flexors in those who presented with mechanical deficits, as opposed to those who only showed functional deficits, thus differentiating between athletes with chronic mechanical instability and chronic functional instability (13).

With regard to active mobility and joint balance, the active range of motion in dorsiflexion is usually impaired after an ankle sprain (14), whereby a lack of mobility predisposes to a recurrence that has been included as a risk factor criterion for developing chronic instability (15). In addition, mobility deficits can negatively influence dynamic postural balance (14), defined as the act of maintaining, achieving or restoring a state of equilibrium during any posture or activity (16).

Along these lines, previous studies and meta-analyses have frequently observed deficits in postural control in patients with CAI, as measured by the Star Excursion Balance test or the Y Balance test. (17) In addition, changes in proprioception and neuromuscular control may be contributory to the development and maintenance of instability. (18,19)

In terms of function, after the development of CAI, 72% of people do not return to their pre-injury level of physical activity and 6% are unable to return to work (10). In this regard, there are different instruments to assess function in the foot/ankle complex, but only two have been suggested by the International Ankle Consortium to assess functional limitations in patients with CAI: the Foot and ankle ability measure (FAAM) and the Foot and ankle Outcome score (FAOS) (20). Although these measures are subjective and based on individual perception of the person's condition, they are very useful in the research setting as they provide important information regarding physical and functional limitation in the context of CAI.

Conservative treatment is the initial therapeutic option for patients with CAI, however, the best strategies are still unclear. Numerous rehabilitation protocols to improve deficits associated with CAI have been examined. These range from simple progressive strength work (21-24) or dynamic postural balance protocols (25-28) to multicomponent rehabilitation approaches

(strength, balance, mobility) (29,30) with effective results in improving strength, balance and function (21-24,28,30-36).

Clinically, a new invasive technique has appeared, known as Percutaneous Ecoguided Neuromodulation (EPMN). This minimally invasive intervention consists of the application of percutaneous electrical stimulation (biphasic square wave electrical current) through an acupuncture needle, as an electrode placed in the vicinity of the nerve or motor point of the muscle to be treated under ultrasound guidance (37), which is hypothesised to generate structural and excitation changes in the nerve, resulting in decreased sensitisation of the nerve. It is an accessible, safe and cost-effective technique for physiotherapists to treat musculoskeletal conditions. To date, there is limited evidence regarding its use. EPMN has been applied for different pathologies with good therapeutic results (38-42), but its use in combination with a multicomponent neuromuscular exercise programme has never been studied.

Therefore, the main objective of the study will be to compare the short- and medium-term effects of an EPMN intervention on the common peroneal nerve together with an exercise programme in relation to pain, ankle range of motion, ankle muscle strength, dynamic balance and function in both performance and self-report in patients with CAI. We hypothesised that those patients who receive neuromodulation combined with the neuromuscular exercise programme will have greater improvements in relation to the variables studied than those subjects who only receive the neuromuscular programme.

METHODOLOGY:

1. Participants:

Adult volunteers from the student body of the Escuela Universitaria Gimbernat Cantabria with a history of ankle sprain and physically active, defined as participation in moderate aerobic physical activity of at least 30 minutes 5 days a week, or vigorous intensity aerobic activity of at least 20 minutes 3 days a week (43), will be assessed to see if they can participate and be included in the study (44).

Inclusion Criteria: Subjects must meet the criteria:

1. History of at least one major ankle sprain. The initial sprain must have occurred at least 12 months prior to study participation, be associated with inflammatory symptoms (pain, oedema) and have resulted in at least one day of interrupted physical activity.
2. The most recent sprain must have occurred at least 3 months prior to study participation.
3. History in the injured ankle of "ankle wandering" (at least 2 episodes in the 6 months prior to study participation) and/or repeated sprains (two or more sprains in the same ankle) and/or feelings of instability in activities of daily living or sports (score less than 24 on the Cumberland Ankle Instability Tool (CAIT).
4. Have a score of less than 75% in three or more categories on the FAOS (Foot and ankle Outcome Score) or a level of less than 90% in activities of daily living or a level of less than 80% in sports activities on the FAAM (Foot and ankle ability measure).

5. Pain on the VAS scale above 3 points out of 10 in physical activity.

Patients will be excluded from the study if they exhibit any of the following criteria:

1. History of surgery on either lower extremity that may interfere with the performance of the tests.
2. History of a fracture of either lower extremity requiring alignment.
3. Acute injury to the musculoskeletal structures of other joints of the lower extremity within the previous 3 months, which impacts joint integrity and function resulting in at least one day of loss of physical activity.
4. Chronic concomitant pathology of the lower extremity (e.g. osteoarthritis, vascular disease, neural pathology).
5. Regular use of antalgic medication that may mask symptoms.
6. Contraindications to percutaneous puncture and to the performance of neuromodulation.
7. Receiving physiotherapy or medical treatment during the operation.
8. Being pregnant at the time of the start of the study.

2. Variables to be studied

2.1 Self-administered scales:

- The Foot and ankle ability measure (FAAM), validated in Spanish (45), is a Likert scale consisting of 29 items, which have a score from 0 to 4, representing different levels of difficulty, divided into two subscales: activities of daily living (ADL) (21 items) and sports (8 items). The values are summed to calculate the score for each subscale, 84 points for ADLs and 32 points for sports (45). For the analysis of the score, the percentage of each subscale is used separately. The test-retest reliability is high, 0.89 for the ADLs and 0.87 for the sports subscale. In fact, the FAAM scale has been shown to be valid for use in patients with ankle instability. (46) It has been suggested that the minimum clinically important difference (MCID) is 8 and 9 points for the ADL subscale and for the sports subscale, respectively. (47)

- The Cumberland Ankle Instability Tool (CAIT), validated in Spanish (48), has been shown to be a valid and reliable tool for assessing functional ankle instability (49). With an intraclass correlation coefficient (ICC) of 0.96, the CAIT scale has demonstrated excellent test-retest reliability. The scale consists of 9 items with a maximum score of 30 points, where higher scores indicate greater stability. It has been suggested that the MCID is 3 or more points (50).

2. 2 Measurements carried out by the therapist:

- Side hop test (SHT): subjects will be asked to jump laterally and medially between two tape marks 30 cm apart 10 times as fast as possible. One repetition is considered a lateral jump of 30 cm and return to the starting position. Two sets shall be performed and the total time in seconds required to complete each set shall be recorded. The time shall be recorded by a hand held stopwatch to the nearest hundredth of a second (ICC 0.84, SEM 2.10 seconds and MDC 5.82 seconds). The rest between sets will be one minute and the lowest time will be used for the study. If a participant falls, puts the contralateral foot on the ground or does not correctly complete the 30 cm distance between lines we consider this as invalid and the participant should repeat the test again. (51)

- Countermovement jump unilateral test (CMJ Unilateral): for this test, subjects will be asked to jump vertically in a standing position with their hands placed on their pelvis. Firstly, there will be a descent phase in which the subjects will bend the knee approximately 90 degrees and then take off as quickly as possible, keeping the lower limb extended during the flight phase. The limb that we do not assess will be kept off the ground at all times. Three repetitions will be performed with a rest of 30 seconds between each one, where we will keep the highest value. The My Jump 2 application installed on an iphone® 11 running iOS 15.1 (Apple Inc., USA) will be used for the measurement. The validity of the application has been found to be high (ICC= 0.997, 95% (Intraclass Coefficient (ICC): 0.996-0.998, P < 0.001) with an almost perfect correlation coefficient (r= 0.995, P< 0.001) between the application and the gold standard, which is a strength platform. Finally, in the reliability analysis, the data are also high (ICC = 0.999, 95% CI= 0.998-0.999, P < 0.001) with an inter-observer difference of 0.1 ± 0.4 cm (52,53).

-Measurement of isometric ankle strength of three muscle groups: invertors, eversors/plantarflexors, invertors/dorsiflexors. Isometric assessment of the ankle in inversion/dorsiflexion and eversion/plantarflexion selectively assesses the tibialis anterior and peroneus longus and peroneus brevis muscles respectively.

For the measurement of isometric strength, participants shall be asked to lie supine with the foot to be measured barefoot on the outside of the stretcher. The starting position of the ankle shall always be neutral. For eversors/plantarflexors a plantar flexion, abduction and pronation movement of the ankle shall be requested and the dynamometer shall be placed on the outside of the foot, just above the head of the fifth metatarsal, for inverters/dorsiflexors a dorsiflexion movement shall be requested, adduction and supination of the ankle and the dynamometer shall be placed on the dorsal medial side above the head of the first metatarsal and finally for inverters, a movement of plantar flexion, adduction and supination of the ankle shall be requested and the dynamometer shall be placed perpendicular to the inner side of the foot. Measurement will be performed with the Microfet2 hand-held pressure dynamometer (Hoggan Scientific, LLC, Salt Lake City UT, USA. (ICC 0.61, 95% CI=0.09-0.81 for dorsiflexors, (54) ICC 0.74, 95% CI= 0.425-0.879 for invertors and ICC 0.84, 95% CI=0.431-0.905 for eversors (55)) in the standardised positions to ensure consistency throughout the study (12,54,55). For this variable, 3 measurements of 5 seconds duration with 20 seconds rest between measurements will be

performed. The value to be taken into account will be the peak isometric force in kg and will be normalised to the body mass of the subjects (12,54).

- Star Excursion Balance Test (SEBT): is a measure of dynamic balance that has been shown to be valid with moderate to good reliability (56). Prior to the SEBT, participants will be instructed on proper reaching technique and allowed 4 practice attempts in each direction until familiar with the procedure, as recommended by Robinson and Gribble (57) and recently updated by Picot et al. (58). Participants will stand barefoot with the first toe in the centre of the crossing of the three lines throughout the procedure. As participants stand on the affected limb, they will be asked to reach as far as possible with the unsupported limb along the reaching direction. Keeping their hands on their hips, participants shall lightly touch the represented line with the most distal part of the outstretched foot and return to a bilateral stance. The distance shall be measured from the centre of the crossing of the lines to the point of greatest reach. A failed test shall be defined as a test in which the participants: a) lift their hands from their hips, b) move or lift any part of the supporting foot or lift the heel, c) transfer weight to the reaching foot when touching the tape measure or contact the ground multiple times or fail to touch the tape at the point of maximum reach and d) fail to return the outstretched foot to the starting position, lose balance or fail to maintain a unilateral stance during the test. Failed tests shall be discarded and reattempted. The maximum distance (centimetres) shall be recorded for each direction of reach. Reach distances shall be normalised to the length of the limb, which shall be measured from the anterior superior iliac spine to the distal end of the medial malleolus. To calculate the composite score, add all the maximum reach distances, divide the sum by 3 times the length of the limb and multiply the quotient by 100. The 3 SEBT directions to be measured are anterior, posterolateral and posteromedial, in support of previous research (ICC intra 0.85-0.91 and ICC inter 0.99-1) with reported minimum detectable change (MDC) values of the normalised reach distance of 5.9% for the anterior direction, 7.8% for the posteromedial direction, and 7.6% for the posterolateral direction (58). Three consecutive measurements shall be made in each direction. The order of the directions shall be randomised.

- Numeric Pain Rating Scale (NPRS): scale used for the assessment of pain intensity, where 0 is no pain and 10 represents maximum pain. (59) There are no data for the MCID in patients with CAI, however, it seems that changes between 1.5 and 2.1 points can be considered as the MCID

for patients with musculoskeletal pain conditions. (60,61). This variable will ask about pain intensity during sports practice.

-Range of Motion (ROM): The range of motion of dorsal ankle flexion will be measured with the My Rom application (version 3.0.4) installed on an iPhone 11 running iOS 15.1 (Apple Inc., USA). Its validity with respect to the Limit® mini digital inclinometer (r = 0.989, 95% CI = 0.986-0.993) and reliability (ICC = 0.976, 95%CI = 0.966- 0.983, Dorsiflex app: (Coefficient of variation) CV = 5.1 ± 2.3%; Digital inclinometer: 185 CV = 4.9 ± 2.5%) has been demonstrated during the loaded lunge test (62).

To measure the dorsiflexion angle, subjects must be placed in a lunge or knight in burden position with the knee flexed and the foot resting on the ground. The device is then placed just below the tibial tuberosity (touching the screen to the subjects' tibia), aligning the z-axis of the phone with the tibia, and then clicking GO on the device screen. Finally, the application will start a 5-second countdown and at the end will record the angle of inclination on the X-axis of the iphone. Three measurements will be taken with a one minute break between measurements.

Before the initial assessment measurements were taken, the subjects completed a 5-minute warm-up of treadmill walking at a self-selected pace plus mobility and muscle activation exercises lasting 3 minutes.

The investigator in charge of the assessments will first examine the pain scale, secondly range of motion, thirdly strength, fourthly balance and lastly function, first with objective tests and finally with self-report tests.

3. Randomisation:

After baseline assessment patients will be randomly assigned to receive a neuromuscular exercise programme (control group) or to receive a neruomuscular exercise programme plus a common peroneal nerve EPMN (experimental group). Concealed allocation will be performed using a computer-generated random table of numbers created prior to data collection by an external investigator. Individualised, sequentially numbered index cards will be prepared. These will be placed in sealed opaque envelopes and the second external researcher will open the envelope and proceed with the treatment according to the allocation.

Each group will be treated by a physiotherapist clinician, who will be the principal investigator of the study, with more than 15 years of experience in the management of lower limb

musculoskeletal injuries and more than 10 years of experience in the management of invasive techniques and ultrasound assessment.

The researcher conducting the data processing will be blinded to group membership and the researchers conducting the assessments will be blinded to the participant's group assignment. Participants in this study will not be blinded to their group assignment. All participants will read and sign an informed consent form prior to inclusion in the study and will be asked to lead a lifestyle identical to the one they were leading prior to the start of the study.

4. Procedures:

Neuromuscular exercise programme:

The combination of strength exercise and dynamic balance exercise has been shown to be more effective than strength work alone in the management of CAI (63). The exercise programme applied in the intervention is based on the best available evidence and is common practice in the clinic. All exercises will be performed under the supervision of the therapist. A 3-week intervention will be performed with two sessions per week.

The strength programme includes a Theraban® protocol as described by Kaminsky et al (23). Participants will sit on the floor with one end of the Theraband® attached to a trellis and the other end attached around the metatarsal head of the foot to be worked on. The knee shall be in full extension and the Theraband shall be initially stretched to 170% of its resting length, regardless of resistance. Strength exercises will include all movements of the ankle (plantar flexion, dorsiflexion, inversion and eversion). The progression of the programme will include an increase in sets (1-3 sets of 8-10 repetitions) or an increase in resistance each week of the intervention depending on the subject's symptomatology (64).

The balance exercise programme will consist of a series of closed kinetic chain exercises in a standing weight-bearing position that will be progressed from bilateral to unilateral depending on load acceptance. The exercises applied in the study will be the bilateral half squat and the unilateral squat with eyes open or closed on a stable surface during the first week. Three sets of 10 repetitions will be performed. The following week the same exercises will be performed, but progressing to an unstable surface. Finally, in the last week, some manual perturbation by the therapist will be included. The focus of all these exercises will be on motor control of the eccentric contractions of the ankle muscles to increase the strength of this musculature and contribute adequately to ankle stabilisation (65).

Ecoguided percutaneous neuromodulation (EPMN):

In addition to the exercise programme, the experimental group will receive a session of EPMN on the common peroneal nerve of the affected lower limb. The EPMN will be applied prior to the exercise programme session. Three interventions will be performed, at a dosage of one per week. It will be performed with the electrostimulator (ES-160 ITO co.). (66) The participant will be placed in prone position with the foot outside the stretcher. The motor part of the common peroneal nerve affecting the innervation of the superficial peroneal nerve will be searched using an ultrasound machine (Chison Echo 5®, Chison Medical Technologies, China) with a high frequency (10 Hz) linear transducer. A dry needle (0.25mmx0.40mm, Agupunt®, Barcelona, Spain) will be introduced until it is close to the perineurium and a square wave biphasic electric current with a frequency of 2 Hz, a pulse width of 250 µsec and a maximum tolerable intensity will be applied on the needle, with the aim of causing visible muscle contraction, according to the protocol of other studies. (37,42) Ten stimulations with a duration of 10 seconds will be performed, with a rest period of 10 seconds between each stimulation. The needle shall be kept still throughout the procedure and the skin shall be cleaned beforehand with isopropyl alcohol and chlorhexidine.

Assessment and follow-up:

The variables under study will be assessed at 3 different points in time: pre-intervention measurement, post-intervention (one week after the intervention), mid-term measurement (one month after the intervention).

Adverse effects:

All patients will be asked to report any type of adverse event they may experience throughout the study and up to one month after completion. An adverse event is defined as a sequela of average duration with any symptom perceived as painful or unacceptable by the participant and requiring treatment (67). As needle insertion in some patients may induce post-treatment discomfort, subjects will be advised to report any incidences. EPMN has adverse effects that are infrequent and not serious, such as post-puncture pain that usually lasts from a few hours to a few days of mild intensity, the possible appearance of a haematoma that will be minimised thanks to the use of ultrasound and pressure techniques on the area, nerve irritation that will be minimised as much as possible by the use of ultrasound again and finally the possibility of infection, so a disinfectant will be used on the area before the technique and single-use gloves. The therapeutic exercise programme has subsequently been used by other research groups and is very safe because it is an incremental programme adapted in intensity individually to each

subject. Possible adverse effects are also rare, where the most common may be increased ankle pain, which will be controlled by adapting the load, the possible generation of delayed onset muscle soreness, which usually has a peak duration of 48 hours and a possible fall with instability and disturbance work, which is minimised by the presence of the therapist monitoring the session at all times.

Sample size calculation:

The sample size and power calculation was calculated with the software G-Power 3.1.9.4 (Heinrich Heine Universität Düsseldorf) (68). Calculations were based on the detection of an 8-point mean difference (MCID) on each FAAM scale (46), assuming a standard deviation of 6.5, a 2-tailed test, an Alpha level of 0.05 and a desired power of 90%. The estimated sample size is 15 participants per group.

Statistical analysis of data:

1. Descriptive data in mean, range and standard deviation.
2. Normal distribution/homoskedasticity of the data (See whether the data are parametric or non-parametric). Kolmogorov-Smirnov test and Levene's test.
3. Comparison of means between two groups (experimental group and placebo control group) using Student's t-test to analyse the differences between the quantitative dependent variables of the study. If the data are non-parametric, we will use the Wilcoxon statistic.
4. Calculate the effect size of the difference between pre and post on the different variables with the cohen's d calculation. A effect size less than 0.2 will be considered trivial, between 0.2-0.5 low, between 0.5-0.8 moderate and greater than 0.8 high.

Data management:

The data will be managed in the following way:

1. Data capture: data will be collected through the data collection notebook which will be obtained by the researcher in charge of the assessments.
2. Classification and storage: each patient will be assigned a control number, in order to maintain the anonymity of the patient over the principal investigator to avoid possible biases. This number will be recorded in a database (Access Sheet) where all patients will be listed in order to identify them in the successive taking of values. This database will

be kept during the execution of the research, and will only be used at the time of data collection, and only the principal investigator of the study will have access to it. Each patient will be identified by this control number and by a code formed by the initials of their first name and their first surname. The data will be stored on the principal investigator's personal computer, access to which is only possible with a username and password available to the same person.

3. Use and treatment: The use is exclusively scientific, without any kind of profit motive. Once the data have been coded, they will be entered into the SPSS statistical package for the corresponding statistical calculation, which will be carried out by the researcher in charge of the analysis. In the dissemination of the results there will be absolute confidentiality of the participant's personal data.
4. Assignment and transfer of data to a third party for processing: No data will be transferred to a third party for processing.
5. Destruction: the data in the collection notebook will be destroyed by a paper shredding machine and the data in the database will be kept for a maximum period of 10 years, after which it will be completely deleted from the researcher's personal computer.

Ethical considerations:

All participants will receive information on the main aspects of the study and will be asked to complete an informed consent form in accordance with applicable law. The procedures to be carried out in this study will follow the ethical standards of the Declaration of Helsinki.

The confidentiality of the data will be guaranteed in accordance with Organic Law 3/2018, of 5 December, on the protection of personal data and guarantee of digital rights.

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