Prediction of response to manual physiotherapy using somatosensory profiles in patients with cervicobrachialgia.

PRINCIPAL INVESTIGATOR: Xabat Casado Zumeta

22.09.2023

TITLE

Prediction of response to manual physiotherapy using somatosensory profiles in patients with cervicobrachialgia.

CODE FOR TRACEABILITY: FST_DCB

PRINCIPAL INVESTIGATOR: Xabat Casado Zumeta

Expected start date: April 2023

Target completion date: April 2024

SUMMARY

Objectives: To know if the evaluation of somatosensory profiles in patients with cervicobrachialgia allows predicting their response to conventional manual physiotherapy.

Methodology: Multicenter clinical trial with a treatment arm. 91 consecutive patients with cervicobrachial pain will be included. 6 manual physiotherapy interventions will be applied together with home exercises of neural sliding, one intervention per week for 6 consecutive weeks. Quantitative sensory evaluations will be performed before and after treatment. The sensory evaluation will include the conditioned pain modulation test, the Offset Analgesia test, and mechanical and thermal sensitivity tests. The primary measurement variable shall be response to treatment according to the GROC scale.

Statistical analysis: An analysis of the change (pre-intervention vs. post-intervention) of the variables of interest will be carried out using the paired t-test for numerical variables and the Wilcoxon test for ordinal or categorical variables. The association between the baseline value of the variables denoting clinical and neurophysiological status and post-intervention symptomatic improvement will be analyzed using binary logistic regression having previously classified patients between responders and non-responders to treatment defined by the GROC scale. A cluster analysis will be performed to identify population subgroups, as well as the response of each subgroup to treatment.

BACKGROUND AND STATE OF THE ART

Cervicobrachial pain (CBP), or the association of neck pain with pain radiating to the upper extremity, has a greater impact on general health and quality of life than isolated neck pain, and causes greater disability (1). These symptoms are a common reason for consultation in patients seeking physical treatment (2).

CBP is a diagnostic challenge for physical therapy, as in many cases it is difficult to demonstrate the presence of neuropathy. A patient with cervical radiculopathy will present with signs of neurological disorder, such as loss of sensation, decreased muscle strength, and/or decreased tendon reflexes. They are all indicative of nervous system involvement. In these cases, electrophysiological tests represent the gold standard for determining the presence of peripheral nerve dysfunction (3). However, it should be remembered that the use of these tests is limited to the analysis of the loss of function of large fibers (A-beta and motor) and completely ignores the pathology of small fibers (A-delta and C), as well as the excitability of the central nervous system (CNS).

Furthermore, CBP is not always associated with nerve conduction disorders or other clear signs of neurological involvement. There are several pathologies with CBP without the presence of concomitant signs of loss of function; pathologies such as referred somatic pain caused by the intervertebral disc (4), referred joint pain (5), referred pain of myofascial origin (6) or neuropathies that occur with radicular pain (7).

This range of possibilities makes diagnosis difficult, as well as the assignment of the most appropriate treatment to each patient.

One of the proposals that have been made to address this heterogeneity in complex clinical conditions is the classification based on neurobiological mechanisms of pain (9). The objective of this methodology is to stratify subjects with the same clinical picture based on the underlying pain mechanisms, with the aim of directing treatment more precisely. Taking this last classification as a starting point, there have been studies that have addressed low back pain associated with pain radiating to the lower extremity (10), in which the authors classified patients based on the concurrent pain mechanisms in each case diagnosed from the clinical manifestations.

Although this approach may be practical from a clinical point of view, it has limitations since it does not quantify the hyper- or hypoexcitability of the nervous system in each subgroup of patients. It seems, therefore, necessary to expand knowledge in this area through new studies that include a more extensive exploration of the aforementioned mechanisms. In this sense, the proposal that several authors have made involves the use of Quantitative Sensory Testing or QST (11,12,13). QST is a non-invasive way to assess sensory perception and pain, and provides information on the different pathophysiological mechanisms involved in central pain processing and allows characterizing the somatosensory profile of each individual and establishing their pain phenotype (14, 15). QST also allows the evaluation of disorders in the function of all types of nerve fibers.

QST is based on the application of controlled sensory stimuli and the quantitative and qualitative evaluation of the sensory perception evoked by these stimuli. Unlike nerve conduction studies, it is a battery of semi-subjective tests since subjective perception is evaluated against controlled stimuli.

In our study we will include the following measures, in order to assess the presence of hyper- or hypoexcitability of peripheral nerve fibers (16):

- The vibration detection threshold, which evaluates the integrity of A-beta fibers.
- The cold detection threshold, which serves to evaluate the function of A-delta fibers.
- The threshold of cold and heat pain, which evaluate the status of subtypes of C fibers.
- The mechanical pressure pain threshold, which serves to evaluate the function of deep sensitivity mechanoceptors.

On the other hand, the presence of CBP can also be a consequence of sensitization at the level of the posterior horn of the spinal cord and/or supramedullary centers of the CNS that by different anti- and pronociceptive mechanisms manifests as an extension of the area perceived as painful

(17, 18). This justifies the inclusion in the study of the central mechanisms, in addition to the peripheral ones. Through so-called dynamic tests, QST also allows the evaluation of the central mechanisms of pain inhibition and facilitation (19). In our study we will include the following:

- We will evaluate the state of the central pain facilitation mechanisms by means of the Temporal Summation of pain test.
- We will evaluate the state of the mechanisms of central pain inhibition using the Conditioned Pain Modulation test and the Offset Analgesia test.

We have identified 3 studies (11,12,13) that included cervical radiculopathy and/or CBP compared to different cases (fibromyalgia, whiplash) and healthy controls in which QST has been used. These studies indicate that patients with cervical radiculopathy and / or CBP, present alterations in the function of small caliber fibers (A-delta and C) and not only in that of thick fibers, justifying the study of these. Interestingly, some studies suggest that this dysfunction may appear before A-beta fibre involvement becomes apparent, and that they may therefore be relevant for early diagnosis (20, 21). This early diagnosis is of special interest for physical therapy, since this subgroup with milder pathology could present predictive or moderating characteristics of the effect, which allows identifying those patients who respond favorably to conservative treatment, before the pathology evolves to a more severe situation.

Conventional physiotherapy treatment (CPT) for CBP, which is part of routine clinical practice, has focused on manual therapy (a set of tissue mobilization techniques, performed by the physiotherapist) together with exercises. Several clinical trials (22,23,24) of varying methodological quality have been identified that support the effectiveness of manual therapy and that have obtained favorable results in relation to subjective patient improvement, pain and disability. Although there is evidence that physical treatments provide significant improvements in pain and disability, it is important to note that there are also studies with negative results (25,26).

One possible explanation for this discrepancy could be the heterogeneity of the peripheral and central pathological mechanisms mentioned above. Likewise, it is unlikely that the same interventions exert a favourable effect on all patients equally in a heterogeneous pathology such as BCD. This suggests subgroups of patients who respond differently to treatment. Identifying patients with the greatest potential to respond favourably to an intervention could improve therapeutic outcomes. Coinciding with this idea, some authors have recommended the approach based on sensory phenotypes (27). However, to date we have not found any physiotherapy studies that have addressed this question.

BIBLIOGRAPHY

1- Daffner S, Hilibrand A, Hanscom B, Brislin B, Vaccaro A, Albert T. Impact of neck and arm pain on overall health status. Spine 2003;28: 2030–2035.

2- Gangavelli R, Sreekumaran Nair N, Bhat AK, Solomon JM. Cervicobrachial pain - How often is it neurogenic? J Clin Diagnostic Res. 2016;10(3):14–6.

3- Schmid AB, Hailey L, Tampin B. Entrapment Neuropathies: Challenging Common Beliefs With Novel Evidence. J Orthop Sports Phys Ther. 2018;48(2):58–62.

4- Slipman CW, Plastaras C, Patel R, Isaac Z, Chow D, Garvan C, et al. Provocative cervical discography symptom mapping. Spine J. 2005;5(4):381–8.

5- Cooper G, Bailey B, Bogduk N. Cervical zygapophysial joint pain maps. Pain Med. 2007;8(4):344–53.

6- Fernández-De-Las-Peñas C, Gröbli C, Ortega-Santiago R, Fischer CS, et al. Referred pain from myofascial trigger points in head, neck, shoulder, and arm muscles reproduces pain symptoms in blue-collar and white-collar workers. Clin J Pain. 2012;28(6):511–8.

7- Hall TM, Elvey RL. Nerve trunk pain: Physical diagnosis and treatment. Man Ther. 1999;4(2):63–73.

8- Bogduk, N. On the definitions and physiology of back pain, referred pain, and radicular pain. Pain 2009;147:17-19.

9- Vardeh D, Mannion RJ, Woolf, CJ. Toward a mechanism-based approach to pain diagnosis. Journal of Pain 2016;17:50-69.

10- Schäfer A, Hall T, Briffa K. Classification of low back-related leg pain. A proposed patho-mechanism-based approach. Man Ther. 2009;14(2):222–30.

11- Tampin B, Slater H, Hall T, Lee G, Briffa NK. Quantitative sensory testing somatosensory profiles in patients with cervical radiculopathy are distinct from those in patients with nonspecific neck-arm pain. Pain 2012;153(12):2403–14.

12- Moloney N, Hall T, Doody C. Divergent sensory phenotypes in nonspecific arm pain: Comparisons with cervical radiculopathy. Arch Phys Med Rehabil 2015;96(2):269–75.

13- Ottiger-Boettger K, Ballenberger N, Landmann G, Stockinger L, Tampin B, Schmid A. Somatosensory Profiles in Patients with non-Specific Neck-Arm Pain with and without positive Neurodynamic Tests. Musculoskelet Sci Pract. 2020;50:102261.

14- Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: A comprehensive protocol for clinical trials. Eur J Pain. 2006;10(1):77.

15- Baron R, Maier C, Attal N, Binder A, Bouhassira Di, Cruccu G, et al. Peripheral neuropathic pain: A mechanism-related organizing principle based on sensory profiles. Pain. 2017;158(2):261–72.

16- Pfau DB, Geber C, Birklein F, Treede RD. Quantitative sensory testing of neuropathic pain patients: Potential mechanistic and therapeutic implications. Curr Pain Headache Rep. 2012;16(3):199–206.

17- Yarnitsky D. Role of endogenous pain modulation in chronic pain mechanisms and treatment. Pain. 2015;156(4):24–31.

18- Treede RD. Gain control mechanisms in the nociceptive system. Pain. 2016 Jun;157(6):1199-1204.

19- Szikszay TM, Lévénez JLM, von Selle J, Adamczyk WM, Luedtke K. Investigation of correlations between pain modulation paradigms. Pain Med. 2021 Sep 8;22(9):2028-2036.

20- Schmid AB, Bland JDP, Bhat MA, Bennett DLH. The relationship of nerve fibre pathology to sensory function in entrapment neuropathy. Brain. 2014;137(12):3186–99.

21- Tamburin S, Cacciatori C, Praitano ML, Cazzarolli C, Foscato C, Fiaschi A, et al. Median Nerve Small- and Large-Fiber Damage in Carpal Tunnel Syndrome: A Quantitative Sensory Testing Study. J Pain 2011;12(2):205–12.

22- Coppieters M, Karel H. Stappaerts, Leo L. Wouters y Koen Janssens. The inmediate effects of a cervical lateral glide treatment technique in patients with neurogenic cervicobrachial pain. J. Orthop Sports Phys Ther 2003;33:369-378

23- Nee RJ, Vicenzino B, Jull GA, Cleland JA, Coppieters MW. Neural tissue management provides immediate clinically relevant benefits without harmful effects for patients with nerve-related neck and arm pain: a randomised trial. Journal of Physiotherapy 2012;58:23-31

24- Rodríguez-Sanz D, Calvo-Lobo C, Unda-Solano F, Sanz-Corbalán I, Romero-Morales C, López-López D. Cervical lateral glide neural mobilization is effective in treating Cervicobrachial pain: A randomized waiting list controlled clinical trial. Pain Med. 2017;18(12):2492–503.

25- Calvo-Lobo C, Unda-Solano F, López-López D, Sanz-Corbalán I, Romero-Morales C, et al. Is pharmacologic treatment better than neural mobilization for cervicobrachial pain? A randomized clinical trial. Int J Med Sci. 2018;15(5):456–65.

26- Kuijper B, Tans JTJ, Beelen A, Nollet F, De Visser M. Cervical collar or physiotherapy versus wait and see policy for recent onset cervical radiculopathy: Randomised trial. BMJ. 2009;339(7727):952.

27- Jesson T, Runge N, Schmid AB. Physiotherapy for people with painful peripheral neuropathies: a narrative review of its efficacy and safety. PAIN Reports. 2020;5(5):1-e834.

28- Fernández-de-Las Peñas C, Ortega-Santiago R, de la Llave-Rincón AI, Martínez-Perez A, Fahandezh-Saddi Díaz H, Martínez-Martín J, Pareja JA, Cuadrado-Pérez ML. Manual Physical Therapy versus Surgery for Carpal Tunnel Syndrome: A Randomized Parallel-Group Trial. J Pain. 2015 Nov;16(11):1087-94.

29- Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. J Man Manip Ther. 2009;17(3):163-170.

30- Ortega A, Alfonso J, Martínez D, Alberto D, Ruiz R. Validation of the spanish versión of the neck disability index. Spine 2010;35(4):114-118.

31- Young I, Dunning J, Butts R, Mourad F, Cleland J. Reliability, construct validity and responsiveness of the neck disability index and numeric pain rating scale in patients with mechanical nek pain with upper extremity symptoms. Physiotherapy Theory and Practice 2019;35(12):1328-1335.

32- Cuesta-Vargas AI, Roldan-Jimenez C, Neblett R, Gatchel RJ. Cross-cultural adaptation and validity of the Spanish central sensitization inventory. Springerplus. 2016 Oct 21;5(1):1837.

33- Freynhagen R, Baron R, Gockel U, et al. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr MedRes Opin. 2006;22:1911–1920.

34- De Andrés, J., Pérez-Cajaraville, J., Lopez-Alarcón, M. D., López-Millán, J. M., Margarit, C., Rodrigo-Royo, M. D., ... & Pérez, M. (2012). Cultural adaptation and validation of the painDETECT scale into Spanish. The Clinical journal of pain, 28(3), 243-253.

35- Cleland J, Fritz J, Whitman J, Palmer J. The Reliability and Construct Validity of the Neck Disability Index and Patient Specific Functional Scale in Patients With Cervical Radiculopathy, Spine. 2006;31(5),598-602.

36- Gómez-Pérez L, López-Martínez AE, Ruiz-Párraga GT. Psychometric Properties of the Spanish Version of the Tampa Scale for Kinesiophobia (TSK). J Pain. 2011 Apr;12(4):425-35.

37- García Campayo J, Rodero B, Alda M, Sobradiel N, Montero J, Moreno S. Validation of the Spanish version of the Pain Catastrophizing Scale in fibromyalgia. Med Clin (Barc). 200818;131(13):487-92.

38- Castro MM, Quarantini L, Batista-Neves S, Kraychete DC, Daltro C, Miranda-Scippa A. Validity of the hospital anxiety and depression scale in patients with chronic pain. Rev Bras Anestesiol. 2006;56(5):470-7.

39- Marije L.S. Sleijser-Koehorst, Michel W. Coppieters, Rob Epping, Servan Rooker, Arianne P. Verhagen, Gwendolyne G.M. Scholten-Peeters. Diagnostic accuracy of patient interview items and clinical tests for cervical radiculopathy. Physiotherapy. 2021;111:74-82.

40- Lee, M., McPhee, R. and Stringer, M. An evidence-based approach to human dermatomes. Clin. Anat. 2008 21: 363-373.

41- Wainner Rs, Irrgang JJ, Boninger ML, Delitto A, Allison S. REliability and diagnostic accuracy of the clinical examination and patient self report measures for cervical radiculopathy. Spine 2003;28(1):52-62.

42- Lemeunier N, da Silva-Oolup S, Chow N, Southerst D, Carroll L, Wong JJ, Shearer H, Mastragostino P, Cox J, Côté E, Murnaghan K, Sutton D, Côté P. Reliability and validity of clinical tests to assess the anatomical integrity of the cervical spine in adults with neck pain and its associated disorders: Part 1-A systematic review from the Cervical Assessment and Diagnosis Research Evaluation (CADRE) Collaboration. Eur Spine J. 2017 Sep;26(9):2225-2241.

43- Nee RJ, Jull GA, Vicenzino B, Coppieters MW. The validity of upper-limb neurodynamic tests for detecting peripheral neuropathic pain. J Orthop Sports Phys Ther. 2012 May;42(5):413-2444-
Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: A comprehensive protocol for clinical trials. Eur J Pain. 2006;10(1):77.

44- Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: A comprehensive protocol for clinical trials. Eur J Pain. 2006;10(1):77.

45- Carlesso LC, Macdermid JC, Santaguida LP. Standardization of adverse event terminology and reporting in orthopaedic physical therapy: application to the cervical spine. J Orthop Sports Phys Ther 2010;40(8):455-63.

46- MacDermid JC, Walton DM, Avery S, et al. Measurement properties of the neck disability index: a systematic review. J Orthop Sports Phys Ther 2009;39:400-17.

47- Cleland JA, Childs JD, Whitman JM. Psychometric properties of the Neck Disability Index and Numeric Pain Rating Scale in patients with mechanical neck pain. Arch Phys Med Rehabil 2008;89:69-74.

48- Cleland JA, Childs JD, Fritz JM, et al. Development of a clinical prediction rule for guiding treatment of a subgroup of patients with neck pain: use of thoracic spine manipulation, exercise, and patient education. Physical therapy 2007;87:9-23.

49- Peduzzi P, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996;49:1373-9.

OBJECTIVES

- To establish whether classification based on mechanisms and somatosensory profiles allows to identify a subgroup of patients suffering from CBP that responds more effectively to CPT.
- To establish the effectiveness of CPT in reducing symptoms in CBP.
- To establish the effectiveness of CPT for the normalization of dysfunctions detected in clinical examination, somatosensory evaluation and endogenous modulation systems.
- To establish whether symptomatological reduction is associated with the normalization of dysfunctions detected in clinical examination, somatosensory evaluation and endogenous modulation systems.

HYPOTHESIS

- A subgroup of patients will be identified among the different somatosensory profiles that present significant differences in the effectiveness of the CPT.
- CPT will be associated with a positive impact on symptom reduction in patients with CBP.
- The CPT will be effective for the normalization of the dysfunctions detected in the clinical examination, the somatosensory evaluation and the endogenous modulation systems.
- There will be an association between the normalization of dysfunctions found in clinical examination, somatosensory evaluation and endogenous modulation systems with symptomatological reduction.

METHODOLOGY

STUDY DESIGN:

Multicenter experimental study without control group. Single arm clinical trial.

STUDY SUBJECTS:

Inclusion criteria:

- Unilateral cervicobrachial pain in subjects between 18-80 years.

Exclusion criteria:

- Signs of severe disease, cervical myelopathy, tumor, rheumatic diseases or a neurological pathology of central origin.
- Cervicobrachial pain of traumatic origin or as a result of whiplash.
- Previous surgical intervention of the cervical spine.

INTERVENTIONS:

The treatment to be applied to all patients is part of the CPT used in routine clinical practice and includes the following:

- Techniques of passive cervical mobilizations and the anatomical structures surrounding the nerve. These techniques will be performed based on the clinical reasoning and irritability of the picture presented. This treatment has shown effectiveness in different clinical trials (22,23,24,28).
- Home exercises of cervical mobility and neurodynamic sliders of the upper extremity. These exercises have been shown to be effective in clinical trials in patients with BCD. (22,23)

ANALYZED OUTCOMES AND MEASUREMENT SCALES:

The first 3 variables described (GROC, NDI and NPRS) will be considered as outcome variables, while the rest will be used as predictor variables. GROC will also be considered as the primary outcome variable.

Sociodemographic data: sex, age, duration of symptoms in weeks, weight, height, work status, number of treatment sessions in the last 12 months.

1.- The subjective improvement described by the patient through the **Global Rating of Change Scale (GROC).**

It is a self-administered questionnaire that aims to measure the degree of subjective improvement from the first intervention received (29). The questionnaire presents a score of 7 positive items to evaluate the subjective improvement of the patient progressively. It also presents 7 negative items to evaluate if the patient has worsened. The 0, is defined as there is no improvement or worsening, the patient is the same. The +7 would mean that the patient would feel much better and the 1 a slight improvement. In the same way, the -7 would indicate that the patient has worsened a lot since the first intervention and the -1, a slight worsening.

2.- The neck disability index (NDI).

It is a one-dimensional questionnaire consisting of 10 sections on different activities and measuring functionality (30). Each section scores from 0 to 5, with 0 being no pain and 5 being the worst pain imaginable (maximum 50 points). Therefore, in order of appearance, of the 6 options the first option of each item represents 0 and the last 5. The score must be multiplied x2 to be expressed as a percentage (%). A 5-point (10%) change from baseline is required to consider clinically meaningful improvement.

3.- The Numeric Pain Rating Scale (NPRS)

Neck and arm pain will be evaluated with the NPRS (31). It is a growing scale that goes from 0 to 10 and that serves to quantify subjectively the pain presented by the patient. 0 is considered as no pain and 10 would be the worst pain imaginable.

4.- Central Sensitization Inventory (CSI)

It is a 25-item questionnaire to assess the presence of signs and symptoms consistent with central sensitization (32). In Part A of the CSI, participants should report the frequency of signs and symptoms present on a scale of 0 (never) to 4 (always). The individual score of each item is added to obtain a total score from 0 to 100, where higher scores indicate greater severity. In Part B, participants should indicate whether they have been diagnosed with one of the 10 central sensitization syndromes described. The presence of one or more central sensitization syndromes suggests higher levels of sensitization.

5- Pain Detect Questionnaire (PD-Q).

It is a questionnaire consisting of temporal and spatial descriptors of pain, and sensory descriptors. The PD-Q classifies patients into 3 groups, as follows (33,34):

- The result is negative = The neuropathic pain component is unlikely. (Score from 0 to 12).
- The result is unclear = The result is ambiguous, however, the neuropathic pain component may be present (Score 13 to 18).
- Positive result = Neuropathic pain is likely (score 19 to 38).

The most severe and average pain intensity over the past 4 weeks is recorded in an NPRS (0 no pain, 10 maximum pain) as part of the PD-Q.

6.- Patient Specific Functional Scale (PSFS)

It is a scale that measures the functional status of the patient by asking about activities that are difficult to perform based on their condition and scoring the level of limitation of each activity. In a study by Cleland et al. (35), they obtained favorable results of the PSFS in terms of validity and reliability in patients with cervical radiculopathy.

7.- Tampa Kinesiophobia Scale (TSK-11)

The Spanish version of the TSK-11 is an 11-item questionnaire developed to identify fear of relapse caused by movements or activities. Items are scored on a four-point scale ranging from "strongly disagree" (1 point) to "strongly agree" (4 points). High scores indicate increased fear of pain/relapse due to movements or activities. The instrument showed good reliability (internal consistency and stability) and validity (36).

8.- Pain Catastrophization Scale (PCS)

The Spanish version of the Pain Catastrophization Scale (PCS) is a 13-item questionnaire developed to identify catastrophic thoughts or feelings in relation to painful experiences. Each item is scored on a five-point Likert scale ranging from "not at all" (0 points) to "all the time" (4 points). The total score can range from 0 to 52 and high scores indicate the presence of more catastrophic thoughts. The Spanish version of the PCS showed adequate psychometric properties, as well as adequate internal consistency and test-retest reliability (37).

9.- Scale for sleep quality.

An increasing scale of 0-10 will be used to assess sleep quality. On the scale, 0 is considered poor sleep quality as a result of their pain and 10, no alteration to fall asleep.

10.- Hospital Anxiety and Depression Scale (HADS)

HADS is one of the most widely used tests to detect emotional distress in non-psychiatric hospital patients with physical illness. It is an instrument consisting of 14 items that has shown its reliability and validity in patients with chronic pain (38). Items are scored on a four-point scale ranging from "always or all day" to "never."

11.- Clinical examination

The clinical examination will include a detailed history taking into account interview items published by other studies (39). They include the following:

- Sociodemographic data: sex, age, duration of symptoms in weeks, weight, height, work status, number of treatment sessions in the last 12 months.

- Clinical data: pharmacological treatment, paresthesia, numbness or loss of strength, movements/positions that aggravate or decrease pain.

In addition to the interview, a neuromusculoskeletal examination will be carried out that will include:

Basic neurological exam:

- **Sensitivity to touch**: The sensitivity to touch of the different dermatomes involved in the upper extremity will be evaluated by means of a piece of cotton and with a toothpick by means of the neuropen. The sensitivity of the healthy limb will be compared with that affected at the following points involving the following dermatomes (40):
    - C3: Suboccipital zone and supraclavicular fossa.
    - C4: Upper trapezius zone.
    - C5: Region bounded by the deltoid.
    - C6: Lateral aspect of the middle and lower third of the arm and anterolateral aspect of the forearm. Including palmar and dorsal face of thumb and forefinger.

- C7: Lateral aspect of the forearm including palmar and dorsal aspect of the thumb, index and middle finger.
- C8: Hypothenar eminence and ulnar zone of the palm and back of the hand.
- T1: Medial aspect of forearm
- T2: Posteromedial face of the arm.

In the first place, a control examination will be carried out in the healthy limb and later it will be carried out in the affected limb. The patient should tell us if there are alterations in sensitivity and if he perceives the stimulus in a more noticeable, similar or lesser way. Results will be noted as hyperesthesia, normoestesia, or hypoesthesia.

- **Myotatic reflexes of the upper extremity**: The reflex hammer will be used to evaluate the response of the roots of C5 and C6 by percussion in the biceps tendon and percussion in the triceps tendon for the evaluation of the roots of C6 and C7. The healthy and affected limb will be examined and compared for asymmetries indicating pathology. The response obtained will be classified based on the observed quality as follows:

    - No answer: muscle contraction is neither palpable nor visible.
    - Normal response: Mild contraction of muscles is accompanied by minor joint movement.
    - Hyperactive reflex: Very strong vigorous muscle contraction is accompanied by exaggerated joint movement, usually associated with clonus.

- **Myotomes**: The loss of strength in the following movements will be manually examined that would indicate a loss of function of the following nerve roots.

    - C5: Shoulder abduction
    - C6: Elbow Flexion + Wrist Extension Test
    - C7: Elbow Extension + Wrist Flexion
    - C8: Finger flexion + Thumb abduction.
    - T1: Abduction of the index.

Orthopedic tests:

The following orthopedic tests that have demonstrated predictive value for the diagnosis of cervical radiculopathy will be used (41,42).

- Spurling test: It consists of performing a homolateral inclination that aims to reduce the intervertebral foramen along with a compression. The test is considered positive with reproduction of symptoms.
- Distraction test: It consists of slightly pulling the cervical spine with the patient in supine position. The reduction of symptoms during the test is considered positive.
- Extension + rotation test: With the patient in supine position, an extension and homolateral rotation is performed. The reproduction of the symptoms suggests facet involvement in the patient's clinical picture.
- ROM in rotation: The patient will be asked to perform a bilateral active rotation. Limitation of mobility to the symptomatological ipsilateral side will be considered positive.

Examination of increased mechanosensitivity of nervous tissue.

- It will be evaluated using neurodynamic tests of the upper extremity (ULNT1, ULNT 2 and ULNT 3) and palpation of the median, radial and ulnar nerves. ULNTs are passive brachial plexus and nerve provocation tests to be evaluated performed supine, involving a sequence of movements that gradually add tension to the nerve trunk. For example, ULNT 1 is performed with: mild scapular depression, shoulder abduction, forearm supination, wrist and finger extension, external shoulder rotation, and elbow extension. Because of the anatomical differences in the path of each nerve, each test is performed by sequencing different movements. The test will be considered positive with reproduction of arm symptoms at least partially and with the presence of structural differentiation. Structural differentiation involves modifying some of the movements of the sequence away from the area of onset of symptoms. It is a feature frequently used to

involve nerve tissue in the symptoms reproduced (43). Palpation of the nerve will be performed by gentle digital palpation of the median, ulnar, or radial nerve at its interfaces. It will be qualified as painful or not painful.

12.- Body mapping of symptoms

The participant will be asked to indicate, on an electronic body map, the location of their symptoms.

13.- Static QST.

Part of the QST protocol standardized by the German Research Network on Neuropathic Pain (44) will be applied by a researcher in a laboratory with constant room temperature. This protocol includes all somatosensory modalities that are mediated by different primary afferents (A-beta, A-delta, C). QST measurements will be taken in the area of maximum pain described by the patient and in the same area of his contralateral side, as well as in a remote area.

As parameters can vary significantly between body areas, comparative baseline data will be obtained in healthy subjects (n=40) from all areas examined. Healthy controls will be matched in terms of age and sex with the cases and will be recruited through word of mouth and/or informational mailing.

The following examinations will be performed:

13.1. Detection and thermal pain thresholds.

The thermal thresholds will be measured using the MSA Thermotest (Somedic) with 9 cm thermode[2]. The device is a peltier type thermal stimulator capable of modifying the temperature of the thermal stimulus in rapid bursts. The reference temperature will be set at 32°C. The cutting temperatures will be 5ºC and 50ºC. All thresholds will be obtained with ramp stimuli (1ºC/sec) that will stop voluntarily when the subject presses a button. Firstly, the cold and heat detection thresholds will be evaluated, and finally the measurement of the cold and heat pain thresholds. The average threshold temperature of 3 valid consecutive measurements will be calculated for each parameter.

13.2. Vibration detection threshold.

It will be measured with a Rydel-Seiffer tuning fork (64 Hz, 8/8 scale). The threshold will be determined as a threshold of disappearance of perception with 3 repetitions of stimuli. Measurements will be taken over bony prominences unless the area of maximum pain does not exhibit a bony surface, in which case, measurements will be taken over adjacent soft tissue. The geometric mean of the 3 measurements will be calculated.

13.3. Pressure pain threshold (PPT).

It will be determined with a pressure algometer with a contact surface of 1 cm^2 and a ramp speed of 50kPa/s (Somedic). Subjects will be asked to press a button when the sensation changes from pressure to pressure pain. The average value of the measurements in triplicate shall be used for the analysis.

14.- Dynamic QST.

14.1. Temporal summation of pain.

It will be measured by a repetitive pinprick stimulus at a controlled intensity using the set of pinprick stimulators (MRC systems). The device is similar to a calibrated pen with a small filament at its end that is capable of applying the same puncture pressure each time it is applied and that makes it impossible to apply a greater force.

The ratio of Wind-Up (WUR) to repetitive puncture stimuli will be measured. The perceived magnitude of a single puncture stimulus (256mN) will be compared to that of a series of 10

puncture stimuli of the same force repeated at a rate of 1/sec. Repeated stimuli will occur within an area of 1 cm^2. Subjects will be instructed to rate pain for the first and last stimulus of the 10-puncture series using an NPRS of 0 to 10, resulting in a ratio. The same procedure will be repeated 5 times to obtain a ratio.

14.2. Conditional pain modulation (CPM) (17).

The cold pressor test will be used to evaluate the efficacy of endogenous pain inhibitory mechanisms. Patients will immerse the healthy limb's hand in an insulated container filled with cold water. Subjects should rate cold hand pain with an NPRS from 0 (no pain) to 10 (worst pain imaginable). The water temperature at the beginning will be set to 10ºC, but can be modified if necessary to ensure that a predetermined target pain intensity is reached (5 in the NPRS). A digital thermometer will be placed in the container to measure the water temperature. When submerging the hand, they will be asked to rate the pain from 0 to 10 at 10-second intervals. More ice or water will be added to the container to adjust the water temperature and achieve the target score.

Immediately after keeping the NPRS within the target score for 30 seconds, the test stimulus will be applied. This will be done to ensure that participants can tolerate the conditioning stimulus and complete the exam. The pressure pain threshold (PPT) test will be applied as a test stimulus to determine the potential effect of CPM during the application of the cold stimulus. The PPT will be measured with an algometer (Somedic) applying pressure through a rubber plate of 1 cm2 and at a rate of 50 kPa / sec in the area of maximum pain described by the patient before the test. Participants will need to press a button as soon as the pressure sensation changes to pain. 3 measurements of the PPT will be taken before and during the application of the cold stimulus by means of the cold pressor test. The values of the three repetitions will be used for analysis.

Healthy control participants will undergo the same CPM protocol with the hand contralateral to their dominant hand submerged in the cold water bath.

14.3. Offset Analgesia

Another method for assessing endogenous pain modulation is the phenomenon of offset analgesia (19). The phenomenon is described as a greater decrease in perceived pain intensity than could be predicted by a small decrease in the noxious stimulus. This small decrease in harmful stimulation is established with the same device (MSA Thermotest) and in the same place on the body. The temperature of the thermode at the beginning will be set to 48ºC, but can be modified if necessary to ensure that a predetermined target pain intensity is reached (5 in the NPRS). Pain intensity will be continuously monitored using an NPRS during the course of the test. It consists of the application of 3 thermal stimuli: the first stimulus (T1) is performed at 48ºC for 5 seconds, followed by a stimulus (T2) of 49ºC of seconds and a last stimulus (T3) of 48ºC for 20 seconds.

15. Nuclear magnetic resonance imaging and plain radiography

The patient will be asked for permission to access the tests performed as part of the medical diagnosis, in order to study whether the morphological changes produced by the aging of the patient (baseline situation) can be predictors of the response to treatment.

ADVERSE EVENTS

The characteristics (type, onset, duration and severity) of the adverse events appearing will be studied by means of a specific questionnaire administered in each of the intervention sessions.

An adverse effect will be defined according to the recommendations of Carlesso et al. (45) as the aggravation of existing symptoms or the provocation of other unpleasant sensations after each session.

SAMPLE SIZE AND STATISTICAL ANALYSIS

With regard to the subjective improvement perceived by the patient, those patients who report feeling "quite a bit better", "a great deal better" or "a very great deal better" will be classified as responders (48), and the rest will be classified as non-responders. With regard to the neck disability index, those patients in whom there is a minimum reduction of 10 points (46) (twice the minimum important clinical difference) will be classified as responders; The remaining patients will be classified as non-responders. Finally, with regard to pain intensity, those patients in whom there is a minimum reduction of 2.6 points (47) (twice the minimum important clinical difference) will be classified as responders; The remaining patients will be classified as non-responders.

A univariate analysis will be performed to determine the association of the independent variables with the outcome variables, dichotomized into responders and non-responders. The chi-square test will be used for categorical independent variables and Student's t or Mann Whitney's U for continuous variables. Those variables that in the previous case obtain a p-value < 0.20 will enter a binary multiple logistic regression model. The calibration capacity of the possible models will be evaluated using the Hosmer-Lemershow test. The ability to discriminate through ROC Curves. The ORs and their confidence interval of the possible predictor variables will be presented.

The calculation of the sample size has been carried out with the objective of being able to identify predictive variables of improvement, being the main outcome the improvement evaluated using the global rating of change, dichotomized as detailed in the previous paragraph. We estimate that in this study at least 60% of patients will be classified as responders. Likewise, we think that approximately 5 variables will be selected after the univariate analysis and candidates to be included in the model. Since predictive model development studies establish that it is necessary to have at least 10 events of the dependent variable of interest for each independent variable included in the multivariate logistic regression model (49), a minimum of 83 patients who have completed treatment and relevant assessments will be necessary. We estimate that at most, 10% of patients will leave the study without completing it. Therefore, a total of 91 patients will need to be recruited.

WORK PLAN

The recruitment of patients will be carried out by the Traumatologist Ana Lersundi, in her consultation of the spine unit of the Donostia hospital, and by the rehabilitation doctor Iván Carbajo in his consultation of the rehabilitation unit of the Donostia hospital. Likewise, patients from the Atlas Fisioterapia center and the Matía Foundation who meet the inclusion criteria will be recruited. Patients referred to the unit who meet the inclusion criteria will be informed about the study and their participation will be voluntary.

Those participants who have shown interest, will be summoned for the first time in the clinical consultations (Deusto Physical TherapIker) of the University of Deusto in Donostia to inform them about the study and having signed the informed consent, to be part of the study. All assessments and treatments will be carried out in this location. The place has the space and material necessary for the correct elaboration of the study. Likewise, the place has the authorization as a health center included within a non-health organization of the Department of Health of the Basque Government (Registration entry number: 2022RTE00912069).

The first assessment will be carried out at the first visit in the consultation, after informed consent to be part of the trial. Participants will be re-evaluated at week 6. It is estimated that each assessment will last approximately 2 hours. In the first assessment, data will be collected on all variables, in the second assessment (week 6) all except sociodemographic data and clinical data will be collected again. Finally, a final assessment will be carried out by telephone at week 14 in which data will be collected on pain using NPRS, the subjective improvement described by the GROC and the neck disability index.

The study will be conducted by five physiotherapists. The principal investigator (Xabat Casado) will be responsible for preparing a list of patients, collecting data, taking measurements and assessing all the variables of interest described above as follows:

- In the first instance, the anamnesis and interview will be carried out in which personal data will be obtained (sex, age, etc.) and about their current clinical picture (location of pain in the body map, behavior and duration of symptoms, previous treatments, etc.).
- Static and dynamic QST measurements will then be taken. The patient will be asked to be comfortably in supine position or sitting (depending on access to the patient's painful area) and measurements of detection and thermal pain thresholds and offset analgesia will be carried out using the thermode. Subsequently, measurements of vibration detection thresholds, pressure pain threshold and temporal pain summation will be made. It is expected that the last test to be performed will be the conditioned modulation of pain, since it entails more time of preparation of the necessary material.
- Once the QST measurements have been obtained, the clinical examination will proceed using the basic neurological examination that includes sensitivity to touch, muscle balance and myotendinous reflexes. All these tests are painless for the patient and will allow a time of rest before the next exam to be performed.
- It will continue with orthopedic tests and neural mechanosensitivity tests. Finally, the patient will be asked to complete the different questionnaires and rating scales mentioned.
- The order of the tests and clinical tests may be altered based on the irritability of the clinical picture, being necessary to stop taking measurements and continue with a questionnaire so that the participant can rest.

A second group, composed of 3 physiotherapists (Ion Lascurain, Laura Domínguez and Karin Fouz) will be responsible for carrying out the manual physiotherapy treatment. The participants will establish with these physiotherapists an approximate planning of the weekly treatment sessions to which the participant must attend.

A final physiotherapist (Ander Cervantes) will be in charge of collecting the post-treatment outcome variables.

LIMITATIONS

Interventions cannot be blinded either to the patient or to the physiotherapists in charge of carrying out the treatments. Likewise, those in charge of carrying out the evaluations cannot act under masking conditions.

DATA MANAGEMENT

The management of the collection and processing of the study data will be carried out through the design of a Data Collection Notebook (DCN) in paper format, in which the researchers assigned to this task will enter the source data of each patient participating in the study.

Current legislation will be complied with in terms of data confidentiality protection (Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights). For this, each patient will receive an alphanumeric identification code in the study that will not include any data that allows their personal identification (coded CRD). The principal investigator will have an independent list that will allow the connection of the identification codes of the patients participating in the study with their clinical and personal data. This document will be filed in a secure area of restricted access, under the custody of the Principal Investigator and will never leave the center.

Once the paper DCNs are complete and closed by the principal investigator, the data will be transferred to a Database.

As in the CRDs, the Database will comply with current legislation in terms of protection of data confidentiality (Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee

of digital rights) in which no data that allows the personal identification of patients will be included.

ETHICAL CONSIDERATIONS

The development of the study will be in accordance with the standards of international Good Clinical Practice, the Declaration of Helsinki in its last active amendment and international and national rules and regulations and will not begin until it has obtained the approval by the CEIC of Euskadi and the agreement of the director of said Institution. Any modification of this protocol will be reviewed and approved by the sponsor and must be evaluated by the EIB for approval before including subjects in a modified protocol.

The study will be carried out according to Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee of digital rights with regard to data processing in which no data that allows the personal identification of the subjects will be included, managing the information in a coded manner.

Patients shall be informed orally and in writing of all information relating to the study and adapted to their level of understanding. A copy of the consent form and information sheet will be provided to the patient. The investigator should allow the patient time to inquire about the details of the study.

The preparation of the informed consent form is the responsibility of the researcher. This form must include all the elements required by the International Conference of Harmonization, the regulatory directives in force, and comply with the GCP Standards and ethical principles that have their origin in the Declaration of Helsinki.

The Principal Investigator will keep the original signed informed consent in a secure area of restricted access, under the custody of the Principal Investigator and will never leave the center and will deliver a copy of the signed original to the patient.

PUBLICATION OF THE RESULTS

The results of the trial will be published in scientific publications, whether positive or negative. The researchers will undertake to try to have the results of this study published in the journal with the greatest possible impact, appropriate to the nature of the study and the area of knowledge to which it refers.

Any communication of the results will maintain the anonymity of the participating patients.

The results or conclusions of the study should preferably be communicated in scientific publications before being disclosed to the non-health public. Results of efficacy not yet determined shall not be announced prematurely or sensationally, nor shall they be exaggerated.