J. Phys. Ther. Sci. 29: 801–806, 2017

The Journal of Physical Therapy Science

Original Article

Neural manual vs. robotic assisted mobilization to improve motion and reduce pain hypersensitivity in hand osteoarthritis: study protocol for a randomized controlled trial

Jorge Hugo Villafañe, PhD, MSc[1)*], Kristin Valdes, OTD, OT, CHT[2)], Grace Imperio, MD[1)], Alberto Borboni, Eng, MSc, PhD[3)], Raquel Cantero-Téllez, PhD, PT[4)], Silvia Galeri, MD[1)], Stefano Negrini, MD[1, 5)]

[1)] *IRCCS Fondazione Don Carlo Gnocchi: Piazzale Morandi 6-20121 Milano, Italy*
[2)] *Gannon University, USA*
[3)] *Mechanical and Industrial Engineering Department, University of Brescia, Italy*
[4)] *Physical Therapy Section, Faculty of Health Sciences, University of Malaga, Spain*
[5)] *Department of Clinical and Experimental Sciences, University of Brescia, Italy*

Abstract. [Purpose] The aim of the present study is to detail the protocol for a randomised controlled trial (RCT) of neural manual vs. robotic assisted on pain in sensitivity as well as analyse the quantitative and qualitative movement of hand in subjects with hand osteoarthritis. [Subjects and Methods] Seventy-two patients, aged 50 to 90 years old of both genders, with a diagnosis of hand Osteoarthritis (OA), will be recruited. Two groups of 36 participants will receive an experimental intervention (neurodynamic mobilization intervention plus exercise) or a control intervention (robotic assisted passive mobilization plus exercise) for 12 sessions over 4 weeks. Assessment points will be at baseline, end of therapy, and 1 and 3 months after end of therapy. The outcomes of this intervention will be pain and determine the central pain processing mechanisms. [Result] Not applicable. [Conclusion] If there is a reduction in pain hypersensitivity in hand OA patients it can suggest that supraspinal pain-inhibitory areas, including the periaqueductal gray matter, can be stimulated by joint mobilization.
Key words: Osteoarthritis, Hand, Rehabilitation

(This article was submitted Oct. 23, 2016, and was accepted Jan. 24, 2017)

INTRODUCTION

Pain in osteoarthritis (OA) is considered a complex integration of sensory and cognitive processes involving several abnormal cellular mechanisms at peripheral and central levels of the nervous system[1, 2)]. The peripherally directed therapies may modulate pain perception bilaterally[3–5)]. This hypothesis opens avenues for future research in the modulation of pain pathways, perhaps offering targets to optimize peripheral manual and physical therapies for pain management in hand OA. Furthermore, patients with hand OA who underwent fMRI analysis, showed increased activation in the thalamus, cingulate, frontal and somatosensory cortex as a consequence of central sensitization[6)]. Several studies have reported the outcomes of multimodal approach to central sensitization evaluated by generalized pressure pain hypersensitivity in patients with carpometacarpal (CMC) OA[5, 7, 8)]. Neurodynamic techniques are a form of manual therapy directed to the neural structures through positioning and movement of multiple joints[9)]. In multiple studies, Villafañe et al. examined the outcomes of patients with CMC OA treated with a neural mobilization technique in the median and radial nerves[3, 10, 11)]. Conservative therapy

*Corresponding author. Jorge Hugo Villafañe (E-mail: mail@villafane.it)

has been shown to relieve symptoms for patients categorized with early stages of hand OA disease to stave off surgical interventions either temporarily or in the long term[12–14]. Recent technologies have facilitated the use of robots as tools to assist patients in the rehabilitation process thus maximizing patient outcomes[15]. These robotic tools assist the patient with carrying out exercise protocols, among these devices the glove (Gloreha), may represent a solution for the control group[16].

We hypothesized that these patients would show hypoalgesia of neural mobilization as compared to robotic assisted mobilization. Therefore, the purpose of this randomized controlled trial is to examine the effects of radial, ulnar and median nerve mobilization vs. robotic assisted passive mobilization of the hand on pain in sensitivity, hand function, and analyze the quantitative and qualitative movement of hand in subjects with hand osteoarthritis.

SUBJECTS AND METHODS

This is a double-blind randomized-controlled trial. The patient will sign the informed consent for study and procedures will be conducted according to the Declaration of Helsinki. This research protocol has been approved by the Local Ethical Committee of "IRCCS D.G.F", Italy on 24 February 2016 and is registered with ClinicalTrials.gov (NCT02701335). This trial is financed by the National Health System of Italy (Project Code: GR-2013-02358472).

Our study will include 72 patients, aged 50 to 90 years old of both genders, with a diagnosis of hand OA. To ensure the precision of results of this trial, subjects who meet the following eligible criteria will be included in this study. All subjects will have OA of the dominant hand. A physiatrist (physician) will establish the diagnosis of hand OA. Each subject will undergo subjective and physical examination performed by a physical therapist experienced in musculoskeletal physiotherapy to evaluate inclusion and exclusion criteria. To be included in the study, the subjects need to have a history of repetitive use of their dominant hand (eg, ex-factory worker) and a diagnosis of hand OA in the dominant hand, according on radiographic findings. The exclusion criteria are: if they score greater than 6 points on the Beck Depression Inventory (BDI) or more than 30 points in the State Trait Anxiety Inventory (STAI)[17]. Patients with a medical history of carpal tunnel syndrome, surgical interventions to the hand, DeQuervain's tenosynovitis, or with degenerative or non-degenerative neurological conditions in which pain perception is altered will be excluded. None of the individuals in this study will have received prior interventions for hand OA.

Recruitment will take place between December 2016 and April 2018. Those who will be considered eligible for the study will be invited for a first interview at which point informed written consent will be completed, inclusion and exclusion criteria confirmed, and a medical history and physical examination will be completed.

Two groups of thirty participants will receive an experimental intervention (neurodynamic intervention plus exercise) or a control intervention (robotic assisted passive mobilization of the hand (Gloreha, Idrogenet, Italy) plus exercise) for 12 sessions over 4 weeks and will be applied to the dominant hand. The variables will be collected in the following order: pain and function (measured by the visual analogue scale, [VAS], pressure pain threshold [PPT] and the Disabilities of the Arm, Shoulder and Hand Score [QuickDASH] questionnaire). Nerve conduction (NC) (measured by the electromyography, [EMG]), and hand mobility (measured by kinematic analysis) will then be assessed. All outcomes measures will be captured at baseline, immediately post-intervention, and at 1- and 3-month post-interventions.

The present document was prepared according to the editorial form of medical publishing and CONSORT publishing rules[18].

Experimental Intervention. Neural mobilization is a maneuver that produces a sliding movement of the neural structures in relation to their anatomical adjacent tissues. A nerve slider is a maneuver producing a sliding movement of the neural structures in relation to their anatomical adjacent tissues. It involves a combination of movement of surrounding so that tension on one end of the nerve increases while the tension on the other end relieves[9].

For the medial nerve, The sequence of movement performed on the patient by the physical therapist for initial positioning for the nerve slider technique is: shoulder girdle depression, glenohumeral abduction and external rotation, supination of the forearm, and wrist, thumb, and finger extension, (Fig. 1a). Then, the nerve slider technique for the median nerve consists of alternating i) the combination of elbow extension (which increases tension on the median nerve) and wrist flexion (which decreases tension on the median nerve) movement with ii) the combination of elbow flexion (decreasing tension) and wrist extension (increasing tension) movement. The imposed range of motion are: i) from 0° to 60° of extension at the wrist, and ii) from 15 to 90° of flexion of the wrist depending on tissue resistance[10].

For the radial nerve, the sequence of movement performed on the patient by the physical therapist for initial positioning consists of shoulder girdle depression, glenohumeral internal rotation, pronation of the forearm, elbow extension, and wrist, thumb, and finger flexion[11]. Finally, ulnar deviation of the wrist is added. The slider neurodynamic technique for the radial nerve consists of alternating the combination of shoulder depression (loads the radial nerve) and elbow flexion-wrist extension (unloads the radial nerve) with shoulder elevation (unloading) and elbow-wrist extension (loading) (Fig. 1b).

Finally, for the ulnar nerve, the wrist is placed in extension, the elbow is flexed and the shoulder abducted. Sliding technique: elbow extension (unloads the ulnar nerve) and shoulder abduction (loads the ulnar nerve) is alternated with elbow flexion (loading) and shoulder adduction (unloading)[19]. Throughout the sliding technique, the wrist is maintained in 60° extension and the forearm in supination (Fig. 1c).

The nerves slider technique will be performed twice for 3 minutes each time with a 1-minute rest between sets. Speed and

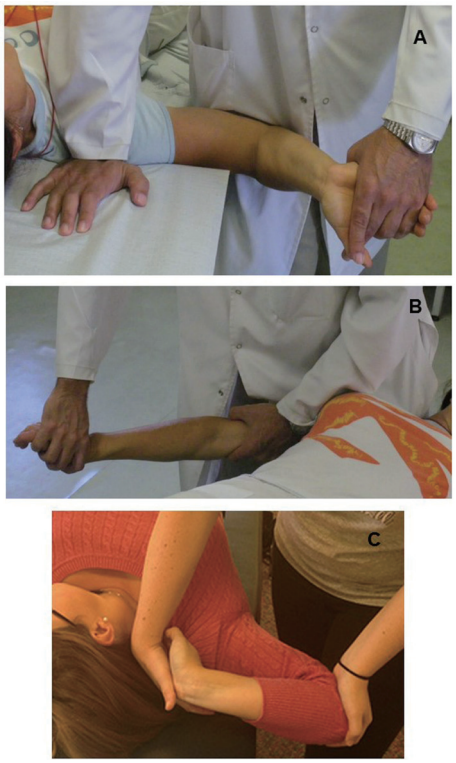

Fig. 1. Nerve slider exercise used to target the median, radial and ulnar nerves

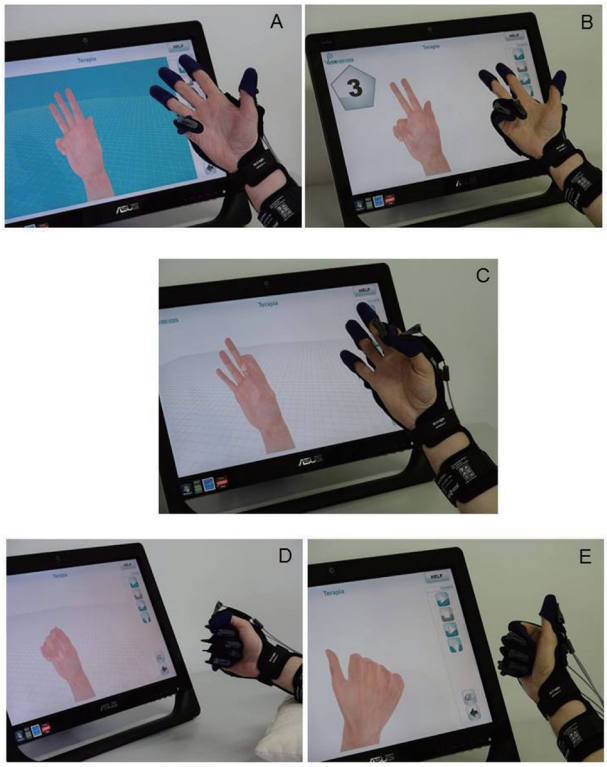

Fig. 2. Hand exercises with Gloreha

amplitude of movement are adjusted such that no pain is produced during the technique.

Control Intervention. Each patient will use the Gloreha device for passive mobilization of the hand twice a day for 4 consecutive weeks. Treatment will include, half an hour of treatment during the morning with the "program" (each finger is mobilized individually) and half an hour of treatment during the afternoon with the "synchronous" (II-III-IV-V finger are mobilized simultaneously, the thumb individually) (Fig. 2). The fingers of the patients are hooked to individual thimbles connectable through a nylon thread to a device fixed on the glove that interfaced with a hybrid system (compressed air and oil) performing the passive movement of flexion-extension of the fingers. The presence of these flexible cables allows the Gloreha glove to gradually moderate the intensity of forces applied on subject's hand and fingers. The length of every cable can be adjusted in the aim to guarantee a progressive and specific adaptation of each finger according to order of the treatment, the type of exercise and the clinical condition of the subject (level of resistance, pain and etc.).

Subjects in both groups will receive the same standardized exercise protocol as described by Villafañe et al[8]. The first 6 exercises consist of active range of motion movements of the hand designed to improve joint flexibility. The remaining 3 exercises are designed to strengthen grip and pinch by using a non-latex polymer ball: the Thera-Band Hand Exerciser (The Hygenic Corporation, Akron, OH, USA) (Table 1). The hand exerciser is color coded based on the approximate resistance provided at 50% compression, with yellow at 0.68 kg, red at 1.36 kg, green at 2.27 kg, and blue at 3.64 kg[20]. All participants started with a yellow ball, and depending on clinical presentation, subjects could be assigned to use more than 1 colored ball. Subjects began with 10 repetitions the first 4 sessions, progressed to 12 repetitions the next 2 sessions, then 15 (2 sessions), and finally 20, if able, during the last sessions[20].

All participants will receive 12 treatment sessions scheduled on separate days, at least 48 hours apart and at the same time of day, 3 days per week, for 4 weeks. Treatment will be only applied to the affected hand.

The outcome measure will be pain intensity of hand, which will be assessed with a visual analogue scale (VAS). (VAS; 0: no pain, 100: maximum pain)[16, 21]. This will be used to assess 3 separate pain status levels: (a) level of pain while executing a grip strength during daily life activities, (b) average level of pain over the last 24 hours, and (c) average level of pain over the last week.

The valid and reliable, QuickDASH questionnaire will be used to measure upper extremity function[22]. It consists of 11 items providing a total score ranging from 0 to 100. Eight items include questions about the ability of the patient to perform certain daily activities, whereas the remaining 3 items are related to upper limb symptoms[23].

Pressure pain threshold (PPT) is a quantitative sensory test of tissue sensitivity and it is defined as the minimal amount of pressure that produces pain, measured via a pressure algometer[24]. PPT will be assessed bilaterally over the hand (first CMC

Table 1. Hand exercises

Exercise	Description
Tabletop	The hand and wrist are held in a neutral position; the subject flexes at the second to fifth meta-carpo-phalangeal (MCP) joints only, and then returns to neutral.
Small fist	From neutral position; the subject flexes at the second to fifth proximal inter-phalangeal joint and distal inter-phalangeal joint only, and then returns to neutral.
Large Fist	From neutral position; the subject flexes all joints to form a fist and then returns to neutral.
Okay signs	From neutral position; the subject flexes to form an ''O'' with the tip of the thumb to the tip of each finger, in turn, returning to neutral after each
Finger spread	From neutral position; hand is placed on flat table top and fingers are spread apart as wide as possible before returning to neutral.
Thumb reach	From neutral position, the subject reaches across the palm of the hand and touches tip of thumb to fifth MCP and then returns to neutral.
Gripping	Subject holds the Thera-Band Hand Exerciser ball in palm of hand and squeezes until ball is about 50% depressed.
Key pinch	Subject holds the Thera-Band Hand Exerciser ball between the side of the thumb and side of the index finger and squeezes until ball is about 50% depressed.
Fingertip pinch	Subject holds the Thera-Band Hand Exerciser ball between the tip of the thumb and the tip of the index finger and squeezes until the ball is about 50% depressed; this is repeated for digits three to five.

at the center of the anatomical snuffbox, and unciform apophysis of the hamate bone), the C5–C6 zygapophyseal joint, the median, ulnar and radial nerves, and tibialis anterior muscle by an assessor blinded to the subjects condition[8].

Nerve conduction (NC) and kinematic analysis of hand. NC will be performed a "Quattro electromyography" (OT Bioelettronica s.n.c, Turin, Italy), with standard techniques, using surface stimulation and recording electrodes. Motor conduction velocity (MCV) and sensory conduction velocity (SCV) of the median, radial and ulnar nerves, will be recorded on both right and left side[25]. Patients will be evaluated by a validated functional test (Action Research Arm Test (ARAT)[26], which measures the patient's ability to perform different tasks of daily living. An investigator will rate each task on a four point ordinal scale (0=unable to perform the task, 3=able to perform the task normally) and the maximal score obtainable is 57 points.

Sixteen retro-reflective hemispheric markers, with diameter of 3 mm will be attached on the affected hand of the subjects in the following bony landmarks: heads of the metacarpals, heads of the proximal phalanges and heads of the middle phalanges of the fingers and the head of thumb metacarpal, head of the proximal phalanx and the head of distal phalanx, and the dorsal tubercle of the radius. The markers configuration is illustrated in Fig. 3.

Subjects will be asked to sit upright in a chair behind a table positioned in front of a Smart-DX optoelectronic system (BTS Bioengineering s.p.a., Milan, Italy) made up of the eight infrared cameras. The chair height and position will be adjusted to provide a 90° of elbow flexion. In the subjects, marker coordinates will be acquired during two dynamic tasks of the hand, shown in Fig. 4: Task 1 (hand grasping a cylinder with a diameter of 40 mm, H4), Task 2 (Primary pinch).

All outcomes measures will be captured at baseline, immediately post-intervention, and at 1- and 3-month post-interventions.

Data will be analyzed using SPSS version 22.0 (SPSS Inc, Chicago, IL, USA), conducted following an intention-to-treat analysis using the last value forward method. After the completion of all baseline measurements, using a computer program (http://www.graphpad.com/quickcalcs/randomize1.cfm), subjects will be randomly assigned by an external assistant into one of 2 groups: an experimental or control group. Group data will be summarized using means and standard deviations. Baseline characteristics of the groups will be compared. Mixed-model analyses of variance will be used to examine the effects of the interventions on each outcome, with the group allotment defined as the between-subject variable and time as the within-subject variable. The sample size and power calculations will be performed with the ENE 3.0 software (GlaxoSmithKline©, Universidad Autónoma, Barcelona). The calculations are based on detecting a mean difference of 2 cm minimal clinically important difference (MCID)[27] on a 10 cm VAS assuming a standard deviation of 2 cm, a 2-tailed test, an alpha level of 0.05, and a desired power of 90%. The estimated desired sample size is 30 individuals per group. To accommodate for expected dropouts before study completion, a total of 36 participants will be included in each group.

DISCUSSION

This protocol was designed to outline the design of an RCT to test whether the presence of widespread pressure pain hypersensitivity and the absence of correlation between symptoms and radiological findings suggest that central sensitization

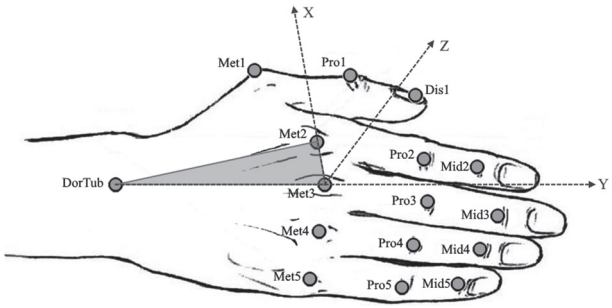

Fig. 3. Markers placement and local reference system

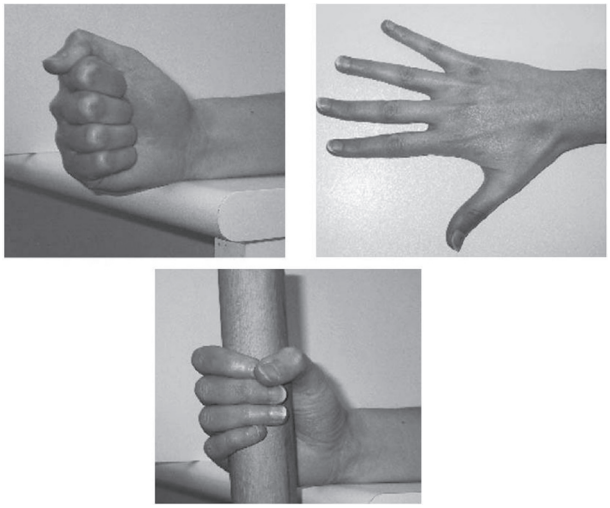

Fig. 4. Tasks analysed in the experimental protocol

mechanisms may play an important role in OA related-pain. We hypothesize that these patients with hand OA will demonstrate a widespread hypersensitivity to mechanical pressure stimuli. We expect to find, like previously in other populations, that the central pain processing mechanisms might be a feature of this pain population[3, 10, 11]. Reliable results allow the professional to reach conclusions that are minimally affected by external factors, thereby reducing the chances of error. This is useful information needed by clinicians to determine the appropriate treatment interventions for patients with hand OA. For treatment to be efficacious, it may need to address the central pain mechanism.

Both the neural manual or robotic assisted mobilization should improve hand range of motion and reduce pain hypersensitivity in the subjects with hand OA. If true, we also expect to know which treatment produced the greatest effect on pain, hand range of motion, and function. Gains in hand range of motion and pain reduction may not equate to increased hand function. This study incorporates subjects' self report assessment of function to determine improvement in the performance of basic self-care activities. If the improvements found are clinically relevant, the carry over of the interventions will be assessed at clinically relevant time points.

This is the first randomized controlled trial to compare the effect of robot-assisted mobilization on the OA hand to therapist provided range of motion exercise. The results of this study can be implemented in clinical practice to help clinicians deal with this challenging patient population. Hand range of motion exercises combined with neural mobilization techniques is a cost effective intervention that may improve hand OA patients' quality of life and function.

Trial status

Recruitment, going to commence in December 2016.

Conflicts of interest

The authors declare that there are no conflicts of interest.

ACKNOWLEDGEMENT

This study was supported by a grant from the Ministry of Health, Italy, 2016, (Project Code: GR-2013-02358472).

REFERENCES

1) Dieppe PA, Lohmander LS: Pathogenesis and management of pain in osteoarthritis. Lancet, 2005, 365: 965–973. [Medline] [CrossRef]
2) Dray A, Read SJ: Arthritis and pain. Future targets to control osteoarthritis pain. Arthritis Res Ther, 2007, 9: 212. [Medline] [CrossRef]
3) Villafañe JH, Bishop MD, Fernández-de-Las-Peñas C, et al.: Radial nerve mobilisation had bilateral sensory effects in people with thumb carpometacarpal osteoarthritis: a randomised trial. J Physiother, 2013, 59: 25–30. [Medline] [CrossRef]
4) Villafañe JH, Fernandez de-Las-Peñas C, Silva GB, et al.: Contralateral sensory and motor effects of unilateral kaltenborn mobilization in patients with thumb carpometacarpal osteoarthritis: a secondary analysis. J Phys Ther Sci, 2014, 26: 807–812. [Medline] [CrossRef]
5) Villafañe JH, Cleland JA, Fernandez-de-Las-Peñas C: Bilateral sensory effects of unilateral passive accessory mobilization in patients with thumb carpometa-

carpal osteoarthritis. J Manipulative Physiol Ther, 2013, 36: 232–237. [Medline] [CrossRef]
6) Sofat N, Smee C, Hermansson M, et al.: Functional MRI demonstrates pain perception in hand osteoarthritis has features of central pain processing. J Biomed Graph Comput, 2013, 3. [Medline]
7) Villafañe JH, Valdes K, Bissolotti L: Thumb carpometacarpal osteoarthritis: are we closer to gold standards? Eur J Phys Rehabil Med, 2016, 52: 907–908. [Medline]
8) Villafañe JH, Cleland JA, Fernández-de-Las-Peñas C: The effectiveness of a manual therapy and exercise protocol in patients with thumb carpometacarpal osteoarthritis: a randomized controlled trial. J Orthop Sports Phys Ther, 2013, 43: 204–213. [Medline] [CrossRef]
9) Butler D, Jones M, Gore R: Mobilisation of the nervous system. Churchill Livingstone, 1991.
10) Villafañe JH, Silva GB, Fernandez-Carnero J: Short-term effects of neurodynamic mobilization in 15 patients with secondary thumb carpometacarpal osteoarthritis. J Manipulative Physiol Ther, 2011, 34: 449–456. [Medline] [CrossRef]
11) Villafañe JH, Silva GB, Bishop MD, et al.: Radial nerve mobilization decreases pain sensitivity and improves motor performance in patients with thumb carpometacarpal osteoarthritis: a randomized controlled trial. Arch Phys Med Rehabil, 2012, 93: 396–403. [Medline] [CrossRef]
12) Bertozzi L, Valdes K, Vanti C, et al.: Investigation of the effect of conservative interventions in thumb carpometacarpal osteoarthritis: systematic review and meta-analysis. Disabil Rehabil, 2015, 37: 2025–2043. [Medline] [CrossRef]
13) Villafañe JH, Valdes K, Berjano P, et al.: Clinical update: conservative management of carpometacarpal joint osteoarthritis. J Rheumatol, 2015, 42: 1728–1729. [Medline] [CrossRef]
14) Villafañe JH, Valdes K: Letter regarding "conservative treatment of thumb base osteoarthritis: a systematic review". J Hand Surg Am, 2015, 40: 1058–1059. [Medline] [CrossRef]
15) Bishop L, Stein J: Three upper limb robotic devices for stroke rehabilitation: a review and clinical perspective. NeuroRehabilitation, 2013, 33: 3–11. [Medline]
16) Bissolotti L, Villafañe JH, Gaffurini P, et al.: Changes in skeletal muscle perfusion and spasticity in patients with poststroke hemiparesis treated by robotic assistance (Gloreha) of the hand. J Phys Ther Sci, 2016, 28: 769–773. [Medline] [CrossRef]
17) Villafañe JH, Valdes K, Angulo-Diaz-Parreño S, et al.: Ulnar digits contribution to grip strength in patients with thumb carpometacarpal osteoarthritis is less than in normal controls. Hand (NY), 2015, 10: 191–196. [Medline] [CrossRef]
18) Johnson C, Green B: Submitting manuscripts to biomedical journals: common errors and helpful solutions. J Manipulative Physiol Ther, 2009, 32: 1–12. [Medline] [CrossRef]
19) Coppieters MW, Butler DS: Do 'sliders' slide and 'tensioners' tension? An analysis of neurodynamic techniques and considerations regarding their application. Man Ther, 2008, 13: 213–221. [Medline] [CrossRef]
20) Rogers MW, Wilder FV: Exercise and hand osteoarthritis symptomatology: a controlled crossover trial. J Hand Ther, 2009, 22: 10–17, discussion 19–20, quiz 18. [Medline] [CrossRef]
21) Jensen MP, Turner JA, Romano JM, et al.: Comparative reliability and validity of chronic pain intensity measures. Pain, 1999, 83: 157–162. [Medline] [CrossRef]
22) Beaton DE, Wright JG, Katz JN, Upper Extremity Collaborative Group: Development of the QuickDASH: comparison of three item-reduction approaches. J Bone Joint Surg Am, 2005, 87: 1038–1046. [Medline]
23) Franchignoni F, Ferriero G, Giordano A, et al.: Psychometric properties of QuickDASH—a classical test theory and Rasch analysis study. Man Ther, 2011, 16: 177–182. [Medline] [CrossRef]
24) Villafañe JH, Silva GB, Fernandez-Carnero J: Effect of thumb joint mobilization on pressure pain threshold in elderly patients with thumb carpometacarpal osteoarthritis. J Manipulative Physiol Ther, 2012, 35: 110–120. [Medline] [CrossRef]
25) Tacconi P, Manca D, Tamburini G, et al.: Electroneurography index based on nerve conduction study data: method and findings in control subjects. Muscle Nerve, 2004, 29: 89–96. [Medline] [CrossRef]
26) Lyle RC: A performance test for assessment of upper limb function in physical rehabilitation treatment and research. Int J Rehabil Res, 1981, 4: 483–492. [Medline] [CrossRef]
27) Emshoff R, Bertram S, Emshoff I: Clinically important difference thresholds of the visual analog scale: a conceptual model for identifying meaningful intra-individual changes for pain intensity. Pain, 2011, 152: 2277–2282. [Medline] [CrossRef]