Journal of Pharmacy and Pharmacology 7 (2019) 124-131
doi: 10.17265/2328-2150/2019.03.005

Pain Exposure Physical Therapy (PEPT) in Complex Regional Pain Syndrome Type 1: A Systematic Review

Nicoli Greco Müller[1] and Glória Maria Moraes Vianna da Rosa[2]

1. Graduated by Centro Universitário IBMR, FVS's Gymnasium Sports Physiotherapy, EFI Physiotherapy, Rio de Janeiro, RJ, Brazil

2. School of Physiotherapy, Serra dos Órgãos University Center (UNIFESO), Teresópolis, RJ, Brazil

Abstract: Complex regional pain syndrome type 1 (CRPS-1) is a debilitating and progressive pathology in which chronic symptoms affect the functional capacity, and there are discussions about its best form of intervention. The aim of this study was to investigate the effectiveness of pain exposure physical therapy (PEPT) on functional recovery of these patients and to compare with conventional treatment. Systematized bibliographic searches were performed with qualitative and quantitative exploratory objective of scientific articles of the last 10 years in the databases PubMed, EBSCO and PEDro. Three studies were selected to analyze: Ek et al. (2009) conducted evaluations at baseline and 3 months after the last session, with 106 patients. The evaluations by Meent et al.'s paper (2011) realized pre-treatment and 12 months after last session, with 20 patients. In Barnhoorn et al.'s article (2015) the only one to perform controlled and randomized study with 56 patients divided into PEPT and conventional, and evaluations were pre-treatment, 3, 6, and 9 months after the last session; performed 5 treatment sessions of 40 minutes, as well as in the other studies. There were positive and significant outcomes on the intervention of PEPT in CRPS-1, showing that this treatment is effective in functional recovery of these patients.

Key words: Reflex sympathetic dystrophy, PEPT, quality of life.

1. Introduction

Complex regional pain syndrome type 1, previously known as reflex sympathetic dystrophy, is a debilitating and progressive condition of one limb, and may become chronic if not identified in the first few months [1, 2].

The cause is not completely understood, but there is great evidence that these patients present a dysfunction in the sympathetic nervous system (SNS) that causes an abnormal reflex. This dysfunction is characterized by continued activity, generating thus an unstable and hyperactive condition of SNS, causing sensory, autonomic, motor and/or trophic changes, progressive ischemia and severe pain. The mechanism of the lesion development and its symptoms involves the performance of the sensory nerves that capture and lead the pain information generated by trauma to the central nervous system (CNS). The pain information activates the SNS that goes to the site of injury acting with inflammatory mechanisms and causing spasm, edema and increased pain. The spasm and pain start a continuous cycle, coming along with great sweat, burning pain and blushing in the affected site [3, 4].

The term "sympathetically independent pain" describes the sensory abnormality of these patients because they do not respond to sympathetic blockade, other than another individual without the CRPS-1 that can present the same painful and sensitive symptoms but respond to the sympathetic blockades, so the symptoms will decrease after the passage of the event that stimulated it [5].

Then, after a trauma, for example, characteristic symptoms arise from three main pathophysiological pathways: intense inflammatory mechanisms,

Corresponding author: Nicoli Greco, higher education in Physical Therapy, Post-graduate in Acupunture and Oriental Medicine, research fields: traumatology and orthopedics.

vasomotor dysfunction and maladaptive neuroplasticity, which will generate sensory, autonomic, motor and trophic changes, leading to severe pain and functional losses consequently [6, 7].

Once the symptoms are installed, patients adopt a protective and avoidance behavior in their daily activities. This creates a cycle of pain-avoidance-disuse-pain, leading to a chronic pain, affecting their motor functions and generating greater compromises to functional incapacity. Patients with chronic pain usually believe that the painful sensation is harmful, then they fear to move the limb and feel the pain. This restriction on movement behavior induced by pain and pain-related fear contribute to the development and establishment of chronic pain related to disability. The fear-avoidance model reproduced by Vlaeyen and Linton in 2000 explains the relationship of the kinesiophobia and CRPS-1 (Fig. 1) [3, 6, 8, 9].

In relation to treatment, Ek et al. mentioned in study published in 2009 works that demonstrate extensive changes in neuroplasticity of the brain of patients with CRPS-1, showing a reduction in the size of the affected limb's representation in somatosensory cortex compared to the healthy side. This distorted image of the body in the brain can lead to a delay in the recognition and control of that injured segment. This will interfere on its motor function and it is one of the reasons that might explain the ineffectiveness of a treatment approach that targets directly and primarily the pain, because patients with chronic pain often introduce resistance to this type of therapy. Physical therapy directed at CRPS-1 was based on a treatment of pain management, respecting it as a sign of injury, not realizing conducts that would spark the painful symptoms, as conventional treatment based on the Dutch 2006 Protocol [8].

Ek et al. observed that the treatment instead of focusing on pain, and yes, directed to the functionality, has proven to be effective in chronic pain, specifically in a therapy called graded exposure treatment (GEXP) (Fig. 1). Through the principles of this treatment pain exposure physical therapy (PEPT) was developed, directed at patients with CRPS-1. PEPT aims to improve functional capacity even with the reproduction of pain. It consists of a progressive-loading exercise program and management of the fear-avoidance-behavior due to pain without using medication. It is based on the assumption that the

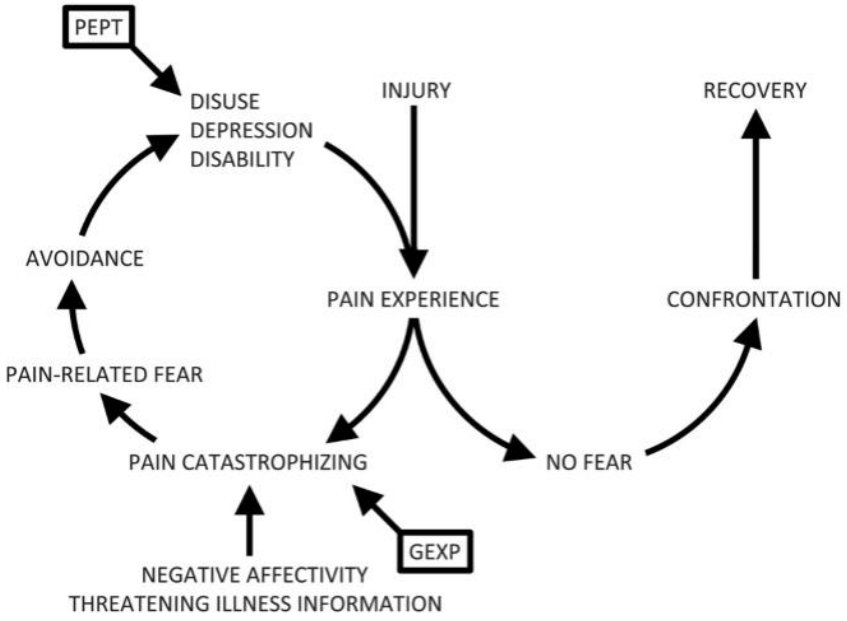

Fig. 1 The fear-avoidance model, showing the targets of (PEPT) and GEXP.
Reproduced from Vlaeyen and Linton in 2000. PEPT = Pain Exposure Physical Therapy. GEXP = Graded Exposure Treatment [10, 11].

exercise program will reduce the peripheral and central sensitivity and regenerate the cortical representation in CRPS-1 [1, 8, 9].

1.1 PEPT-Based Intervention

The difference between PEPT and GEXP is that GEXP is limited to patients with high level of kinesiophobia using a graded hierarchy of fear-eliciting situations for which patients are gradually exposed. In the PEPT approach, the patient is exposed directly to the painful stimulus, without a hierarchy of activities [4].

The initial approach involves guidelines, which is explained to the patient that the persistent complaints of pain are a false alarm of the brain and not a sign of tissue injury [8, 9].

In the first assessment, the entire patient's history is collected to determine his/her main goals. According to this, the intervention is adapted individually. The patient receives detailed information about his/her condition and the content of PEPT [4, 9]

Medications are gradually eliminated [4].

The kinesiotherapeutic conduct is based on progressive loading exercises increasing patient's motivation to carry out the daily tasks, which involve training of muscular strength, passive and active joint mobility exercises; traction and translation of the restrained joints; assisted or active movement combined with passive stretching of hypertonic muscles; If necessary, manual friction of tender points [4, 8, 9].

The goal of these conducts is to increase active and passive range of motion, encouraging patients to ignore the pain sensation, even when it is increased. Patients are motivated to exercise a role of active person, return to your usual life without help and perform their daily tasks, using the affected limb in a functional way [8].

The contraindications include patients with pain and deregulation arising from pseudarthrosis, osteomyelitis, arthritis or osteosynthesis' complications [3, 9].

According to Barnhoorn et al., it was evidenced that PEPT is a promising treatment. Table 1 published in these authors' study, shows the differences between PEPT and the conventional treatment, by the Dutch 2006 Protocol. The first topic is the meaning attributed to pain, being it a false alarm on PEPT and a sign of dysfunction in the conventional treatment. In addition to face-to-face and individual sessions, there are also

Table 1 Description of interventions according to the TIDieR checklist.

	PEPT	Conventional treatment
Why	Pain is a false warning sign Rapidly regaining functional activity, despite levels of pain	Pain is a sign of dysfunction Pain contingent, improving functional activity while controlling pain
What	Exposure to painful movements and activities; No medication, no TENS, no walking aids, splints or bandages; Self-massage, "forced" use, progressive-loading exercises, muscle strength training, joint mobility exercises; Information and education about CRPS-1, PEPT and the role of chronic pain as a false warning sign; Internal locus of control	Dependent of pain limits; Medication (analgesics, free radical scavengers, Ca^{2+} channel blockers, etc.), TENS, walking aids, splints, bandages; Mild exposure, progressive-loading exercises, muscle strength training, joint mobility exercises; Information and education about CRPS-1 and the role of pain as a protective response and a sign of dysfunction; External locus of control
Who provides	Two physical therapists; Partner as a "home coach"	Anaesthesiologist, physical therapist, rehabilitation physician
How	Face-to-face, individually, explicit home exercises and functioning in activities of daily living	Face-to-face, individually
Where	PT department, continuously in daily life	Anaesthesiology department, PT department
How much	Maximum five sessions of 40 min	No predefined limits, on average 15-20 sessions
Tailoring	Adapted to individual competencies and daily life requirements	Adapted to levels of pain

CRPS-1, complex regional pain syndrome type 1; PEPT, pain exposure physical therapy; PT, physical therapy; TENS, transcutaneous electrical nerve stimulation; TIDieR, Template for Intervention Description and Replication [7].

home exercises and functional activities during the daily routine in PEPT's, and its number of sessions is significantly lower. The PEPT adapts the intervention to individual competencies and daily life requirements, and conventional treatment is adapted to levels of pain [4].

Despite the evidence, the treatment of patients with CRPS-1 continues to be a subject of discussion, due to its complex and clinical variability with pathophysiology signs and symptoms, and a difficult diagnosis. Then, the objective of this study was to investigate the effectiveness of PEPT in functional recovery of patients with CRPS-1, and compare it to the conventional treatment based on the Dutch 2006 Protocol.

2. Method and Materials

Searches of scientific articles were undertaken in the following databases: PubMed, EBSCO and PEDro; using the descriptors: "reflex sympathetic dystrophy", "pain exposure physical therapy" and "quality of life".

The inclusion criteria were: articles in English and Portuguese published in the last 10 years; articles that mention or describe the CRPS-1 and the PEPT; and articles that make studies with individuals from 13 years.

Exclusion criteria included articles that cover other topics like studies in amputees and patients involving neurological disorders, for example; non-original articles; with photothermoelectrotherapy as physiotherapeutic approach and those related to pharmacological or biomedical therapies.

The main descriptor used was "reflex sympathetic dystrophy". However, other key words were used, such as "quality of life" and "pain exposure physical therapy". The search strategy used in the PubMed database was the descriptors: "Reflex Sympathetic Dystrophy" and "PEPT" and "quality of life". The search strategy used in the PEDro database was: "pain exposure physical therapy". The search strategy used in the EBSCO database was: "Reflex Sympathetic Dystrophy" and "Pain Exposure Physical Therapy" and "Quality of life".

3. Results

Eight scientific articles were found in databases: 1 in PubMed, 2 in PEDro and 5 in EBSCO. Removed articles that were not accepted for this review: 5 in total, 1 from PEDro and 4 from EBSCO, which reasons for the exclusion includes the following factors: approach in amputees patients, literature review and articles with no intervention. Thus, 3 scientific articles remained, although two of them were found both in PEDro and EBSCO. One paper considered relevant to this work was added. After analysis, considering the objectives proposed in this research, 3 articles were selected (Fig. 2), in which one is demonstrated in Table 2. The results showing of which one were selected based on the relevance they have for this study.

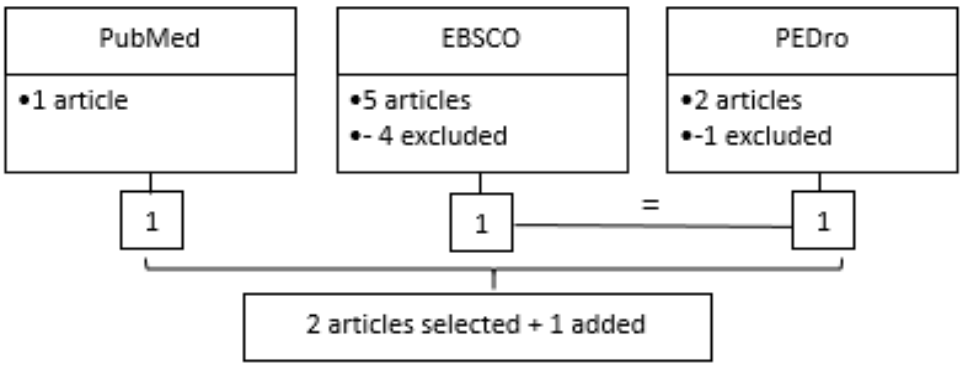

Fig. 2 Results representation.

Table 2 Presentation of the synthesis of articles included in the systematic review.

Database	Added paper (PubMed)	PubMed	EBSCO; PEDro
Authors	Ek et al. [8]	Meent et al. [9]	Barnhoorn et al. [7]
Title	PEPT may be a safe and effective treatment for longstanding complex regional pain syndrome type 1: a case series	Safety of "pain exposure" physical therapy in patients with complex regional pain syndrome type 1	PEPT compared to conventional treatment in complex regional pain syndrome type 1: a randomised controlled trial
Journal	Clinical Rehabilitation 2009	International Association for the Study of Pain; J. Pain 2011	BMJ Open 2015
Objectives	To determine if treatment of longstanding CRPS-1, focusing on functional improvement only while neglecting pain, results in clinical improvement of this syndrome.	To investigate primarily whether PEPT could be applied safely in patients with CRPS-1.	To compare the effectiveness of PEPT with conventional treatment in patients with CRPS-1 in a randomised controlled trial with a blinded assessor.
Methods	Physical Therapy of the affected limb directed at functional improvement only while neglecting the pain was performed following an extensive explanation. Normal use of the limb between the treatments was encouraged despite pain. A maximum of five of these sessions were performed in three months. *n* = 106. Measures at pre-treatment (T1) and 3-4 months after last session (T2).	Medications and other therapies gradually eliminated. The treatment was based on cognitive-behavioral aspects approach, progressive-loading exercise program (focusing on specific body function, passive and active exercises and muscle strengthening), desensitization and in-home workouts. Conssisted of a maximum of 6 treatment sessions of 1hour. *n* = 20. 3 measurements: pre-treatment (A1-4 weeks duration) during the treatment (B-3-4 months duration), and post-treatment (A2-duration 12 months after the last session).	Participants: 56 adult patients with CRPS-1 participated. Three patients were lost to follow-up. Interventions: Patients received either PEPT in a maximum of five treatment sessions, or conventional treatment following the Dutch multidisciplinary guideline. Measurements: Outcomes were assessed at baseline and at 3, 6 and 9 months after randomisation. The primary outcome measure was the Impairment level Sum Score—Restricted Version (ISS-RV), consisting of visual analogue scale for pain (VAS-pain), McGill Pain Questionnaire, active range of motion (AROM) and skin temperature. Secondary outcome measures included Pain Disability Index (PDI); muscle strength; Short Form 36 (SF-36); disability of arm, shoulder and hand; Lower Limb Tasks Questionnaire (LLTQ); 10m walk test; timed up-and-go test (TUG) and EuroQol-5D.

(Table 2 continued)

Database	Added paper (PubMed)	PubMed	EBSCO; PEDro
Authors	Ek et al. [8]	Meent et al. [9]	Barnhoorn et al. [7]
Results	Radboud Skills Test: Limitation score (max. = 40): T1 = 21 (1.39; 4-32); T2 = 5.8 (1.16;0-30) $p <$ 0.0001. Effort score (max. = 20): T1 = 7.8 (0.79; 0-16); T2 = 2.6 (0.5; 0-10) $p <$ 0.0001. VAS pain: T1 = 4.9 (0.24; 0-9); T2 = 2.7 (0.27; 0-9) $p <$ 0.001.	VAS pain: A1 = 58.2 (3.2); B = 38.2 (6.6); A2 = 25.1 (3.1) $p <$ 0.001 (57%). ROM hand: A1 = 100, B = 47.5; A2 = 34 $p <$ 0.001 (66%). Grip strength: A1 = 100; B = 72.4; A2 = 48 $p <$ 0.001 (52%). DASH: A1 = 71.7 (16.2); B = 57.5 (16.3); A2 = 45.7 (18.2) $p <$ 0.001 (36%). PDI: A1 = 37.8 (9.4); B = 28.5 (13.7); A2 = 17.6 (13.5) $p <$ 0.001 (60%). TSK: A1 = 22.7 (5.5); B = 20.4 (5.4); A2 = 18.7 (6.5) $p <$ 0.001 (18%). SF 36-PHC: A1 = 27.6 (21.3); B = 37 (21.2); A2 = 74.3 (21.7) $p <$ 0.001 (269%).	ISS-RV: PEPT) Pt: 21 (5.3); 3 m: 14.94 (5.84); 6 m: 14.86 (6.13); 9 m: 14.3 (5.88) (6.7 pts). CONV.) Pt: 21.12 (5.31); 3 m: 16.43(6.25); 6 m: 15.03(6.35); 9 m: 14.92 (5.28) (6.2 pts). Active ROM: PEPT) Pt: 4.71 (2.16); 3 m: 3.11 (1.26); 6 m: 3.35 (1.67); 9 m: 2.89 (1.22) (1.8 pts). CONV.) Pt: 4.93 (1.98); 3 m: 4.04 (1.95); 6 m: 3.52 (1.26); 9 m: 3.32 (0.95) (1.6 pts). VAS pain: PEPT) Pt: 6.18 (2.5); 3 m: 4.41 (2.85); 6 m: 4.31 (2.81); 9 m: 3.52 (2.69). CONV.) Pt: 7.11 (2.01); 3 m: 5.35 (3.09); 6 m: 4.92 (3.34); 9 m: 4.96 (3.02). McGill Pain Questionnaire: PEPT) Pt: 5.73 (2.11); 3 m: 4.33 (1.97); 6 m: 3.78 (2.30); 9 m: 3.6 (1.7). CONV) Pt: 5.15 (1.43); 3 m: 4.36 (1.91); 6 m: 3.9 (2.05); 9 m: 3.29 (1.88). Skin Temperature: PEPT) Pt: 4.39 (2.91); 3 m: 3.07 (2.39); 6 m: 3.5 (2.52); 9 m: 4.26 (3.15). CONV.) Pt: 3.96 (3.35); 3 m: 3.92 (2.74); 6 m: 3 (2.23); 9 m: 3.32 (2.45) PDI: PEPT) Pt: 36.08 (11.38); 3 m: 22.88 (14.44); 6 m: 14.33 (14.37); 9 m: 14.49 (14.8). CONV.) Pt: 34.12 (14.59); 3 m: 22.92 (15.91); 6 m: 18.37 (14.49); 9 m: 15.94 (15.34). SF-36: PEPT) Pt: 48.17 (15.31); 3 m: 60.9 (17.55); 6 m: 73.98 (13.63); 9 m: 73.3 (17.49). CONV.) Pt: 47.60 (16.85); 3 m: 58.35 (20.73); 6 m: 66.39 (17.42); 9 m: 68.57 (18.9). Muscle strength: PEPT) Pt: 61.9 (22.96); 3 m: 36.8 (27.86); 6 m: 27.5 (26.52); 9 m: 25.83 (27.39). CONV.) Pt: 67.14 (23.16); 3 m: 46.1 (26.16); 6 m: 38.25 (27.2); 9 m: 32.5 (27.22). DASH: PEPT (n = 18) Pt: 57.33 (13.54); 3 m: 37 (17.70); 6 m: 28.79 (19.88); 9 m: 28.57 (19.88). CONV. (n = 19) Pt: 58.27 (12.18); 3 m: 43.45 (22.91); 6 m: 35.59 (21.19); 9 m: 27.52 (22.00).

DASH, Disability of arm, shoulder and hand (points); ISS-RV, Impairment level Sum Score-Restricted Version; PDI, Pain Disability Index; TSK, Tampa Scale of Kinesiophobia; ROM, active range of motion difference between sides of the hand; SF 36-PHC, RAND-SF 36 quality-of-life perceived health change; VAS, visual analogue scale.

4. Discussion

The objective of the first selected article by EK et al. from 2009 was to determine whether the treatment of CRPS-1 in chronic phase, focusing only on the functional improvement while the pain is neglected, results in clinical improvement. The second article of MEENT et al. of 2011, had as its purpose to investigate if PEPT could be applied in patients with CRPS-1 securely. And the last and third one by Barnhoorn et al. from 2015 compares the effectiveness of PEPT with conventional treatment, based on the Dutch 2006 Protocol in patients with CRPS-1, the only controlled trial study found.

In relation to the methods of the studies, the intervention was based on the same principles of PEPT features presented in the introduction of this work. In the first article, evaluations were carried out at baseline and 3-4 months after the last session, n = 106. In 2011 article, the measurements were realized at baseline, during the treatment sessions (which lasted from 4 weeks to 3 months), and 12 months after last session, n = 20. The last study divided equally the 56 participants in conventional treatment group and PEPT group. The

evaluations were taken at baseline, then 3, 6, and 9 months after the last session. Five treatment sessions were performed lasting 40 minutes, as well as in other studies in which the number of sessions was at most five. The conventional group (CONV) performed pharmacological interventions and physical therapy based on pain management.

The scales and measurements taken by the studies and discussed below were selected by the author of this article following the criteria of the upper limb functionality evaluation and quality of life, and other scales considered relevant, expressing significant results and collaborating to this work.

Ek et al. measured the upper limb functionality through the Radboud Skills Test, and it demonstrated in the scale of limitation at baseline a score of 21.0, at a maximum score of 40, and at T2, 3 months after treatment, equal to 5.8; on the scale of effort, T1 equals 7.8, of a maximum score equal to 20, and T2 equals to 2.6. A decrease in scores of these scales gives positive result. The pain assessment by VAS was 4.9 to 2.7.

Among the expressive results of Meent et al.'s study there were VAS scales that revealed a statistically significant improvement of 57% from the baseline until 12 months after the last treatment session (A1 = 58.2; A2 = 25.2, $p < 0.001$). The result of the active range of motion, meaning the difference between sides, decreased 66% ($p < 0.001$). The difference between sides of grasping strength decreased by 52% ($p < 0.001$). The functional upper limb activity evaluated by DASH obtained a 36% improvement ($p < 0.001$). The pain disability index (PDI) has improved 60% when compared the results of A1 to A2—at baseline and 12 months after the end of treatment ($p < 0.001$). Tampa Scale of Kinesiophobia (TSK) had a reduction of 18% from A1 to A2 ($p < 0.001$). The average perceived change in SF-36 health PHC, as a quality of life assessment, between A1 and A2 showed an improvement of 269% ($p < 0.001$).

In the study of Barnhoorn et al., from 2015, according to intention-to-treat analysis, scales that have shown significant results in the comparison between the 2 groups are the ISS-RV, which showed a decrease of 6.7 points at PEPT group and 6.2 points in the conventional group; The difference in active range of motion among the members showed a difference in PEPT Group of 1.8 and Conventional group of 1.6. Other scales as VAS, MQP and skin temperature had significant long-term improvements in both groups, but without significant difference between them. PEPT group patients also showed significant improvement in PDI, and in quality of life (SF-36).

It is worth highlighting the presence of follow-up, of at least 3 months, in the three articles. Despite the fact that the two works, from 2009 and 2011, have no control group, they obtained significant positive results at follow-up, showing that the results were kept, and within a maximum of five treatment sessions over a period that lasted three-month average.

The visual analogue scale, VAS, was measured in the three studies and achieved significant positive results in all of them. In both Meent et al. and Barnhoorn et al.'s works, the scales in common use which also showed positive and significant results during the follow-up, were active ROM, muscle strength, DASH, PDI, TSK and SF-36. Stands out to the amount of measurements outcomes from the 2009 to 2015 study, in which the number of evaluations conducted was very superior to the other studies, which demonstrated a growth and higher quality in terms of evaluation for treatment researches.

It is not possible to ensure the supremacy of PEPT compared to conventional treatment once there is no sufficient evidence to affirm that. There are just few statistically significant differences between all scales examined in the controlled trial, besides the fact of having only one controlled study in this area, which would be very little to assert the superiority of one treatment in relation to the other.

A limitation in the study of Barnhoorn et al. (2015) was the loss of some patients in follow-up and after randomization, and no specific attitude was taken to

compensate for this change.

Despite the evidences above, clinical applicability of PEPT remains restrict because of the lack of adequate professional instructions and only a few studies conducted in this area. However, its knowledge is of extreme importance to incentive the growth and reflections about forms of interventions on pathologies involving chronic pain and functional disability, related to cognitive-behavioral factors.

5. Conclusions

PEPT-based treatment in patients with CRPS-1 brings improvements in functional capacity and reflects on the quality of life of these individuals, with results that can be maintained for at least one year. Although it cannot be considered superior to conventional treatment once there were no statistically significant differences among the majority of scales examined in the controlled study. This way, more studies are needed in this form of approach.

Acknowledgments

To my patient A.L for inspiring me to do this research. To Centro Universitário IBMR, specially the docent Carlos Eduardo Alves for believing and encouraging the presentation of this work in congress and providing us support.

References

[1] Barnhoorn, Karlijn, J., et al. 2012. "The Effectiveness and Cost Evaluation of Pain Exposure Physical Therapy and Conventional Therapy in Patients with Complex Regional Pain Syndrome Type 1. Rationale and Design of a Randomized Controlled Trial." *BMC Musculoskeletal Disorders* 13: 58.

[2] Kisner, C., and Colby, L. A. 2016. *Therapeutic Exercise: Foundations and Techniques*, 6th Edition.

[3] Zakka, T. R M., et al. 2011. "Síndrome complexa de dor regional e gestação. Relato de caso." *Revista Dor São Paulo (SP)* 12 (1): 74-7.

[4] Folberg, C. R., et al. 2011. "Distrofia Simpática Reflexa nas mãos. Clínica da Mão: Cirurgia do membro superior e microcirurgia." Clínica da mão-Porto Alegre (RS)-Brazil. Accessed November 11, 2016 http://www.clinicadamao.com/artigos-categoria/24-distrofia-simpatico-reflexa-nas-maos.

[5] Fernandes, P. V. 2001. "Reflex Sympathetic Dystrophy—RSD." InterFisio. Accessed November 11, 2016. http://interfisio.com.br/?artigo&ID=57&url=Distrofia-Simpatica-Reflexa---DSR.

[6] Barnhoorn, Karlijn, J., et al. 2015. "Are Pain-Related Fears Mediators for Reducing Disability and Pain in Patients with complex Regional Pain Syndrome Type 1? An Explorative Analysis on Pain Exposure Physical Therapy." *PLOS ONE* |DOI:10.1371/journal.pone.0123008.

[7] Barnhoorn, Karlijn, J., et al. 2015. "Pain Exposure Physical Therapy (PEPT) Compared to Conventional Treatment in Complex Regional Pain Syndrome Type 1: A Randomized Controlled Trial." *BMJ* 5: e008283. doi:10.1136/bmjopen-2015-008283.

[8] Ek, J. W., et al. 2009. "Pain Exposure Physical Therapy May Be a Safe and Effective Treatment for Longstanding Complex Regional Pain Syndrome Type 1: A Case Series." *Clinical Rehabilitation* 23: 1059–66.

[9] Meent, H., et al. 2011. "Safety of 'Pain Exposure' Physical Therapy in Patients with Complex Regional Pain Syndrome Type 1." *International Association for the Study of Pain—IASP* 23: 1059–66.

[10] Vlaeyen, J. W. S., and Linton, S. J. 2000. "Fear-Avoidance and Its Consequences in Chronic Musculoskeletal Pain: A State of the Art." *Pain* 85: 317-32.

[11] Leeuw, M., et al. 2007. "The Fear-Avoidance Model of Musculoskeletal Pain: Current State of Scientific Evidence." *Journal of Behavioral Medicine*. doi: 10.1007/s10865-006-9085-0.