American Journal of Physical Medicine & Rehabilitation Articles Ahead of Print
DOI: 10.1097/PHM.0000000000002275

CLINICAL EFFICIENCY OF HIGH-INTENSITY LASER THERAPY IN PATIENTS WITH CERVICAL RADICULOPATHY: A 12-WEEK FOLLOW-UP, RANDOMIZED, PLACEBO-CONTROLLED TRIAL

Songül İNCE *, Nuran EYVAZ, Ümit Dündar, Hasan Toktaş, Hilal YEŞİL, Selma Eroglu, Sevda ADAR

*Department of Physical Medicine and Rehabilitation, Dinar State Hospital, Afyonkarahisar, Turkey

Department of Physical Medicine and Rehabilitation, School of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey

1. Songül İNCE, MD, Physiatrist

Department of Physical Medicine and Rehabilitation, Dinar State Hospital, Afyonkarahisar, Turkey

E-mail: songulince07@gmail.com

Telephone: +90 0553 426 73 85

ORCID: 0000-0002-5006-6409

2. Nuran EYVAZ, Asst. Prof.

Department of Physical Medicine and Rehabilitation, Afyonkarahisar Health Sciences University Hospital, Afyonkarahisar

E-mail: n_eyvaz@hotmail.com

ORCID ID: 0000-0001-7810-9004

3. Ümit DÜNDAR, Prof.

Department of Physical Medicine and Rehabilitation, Afyonkarahisar Health Sciences University Hospital, Afyonkarahisar

E-mail: umitftr@yahoo.com

ORCID ID: 0000-0002-2784-0574

4. Hasan TOKTAŞ, Prof.

Department of Physical Medicine and Rehabilitation, Afyonkarahisar Health Sciences University Hospital, Afyonkarahisar

E-mail: hasantoktas@gmail.com

ORCID ID: 0000-0002-1260-0412

5. Hilal YEŞİL, Assoc. Prof.

Department of Physical Medicine and Rehabilitation, Afyonkarahisar Health Sciences University Hospital, Afyonkarahisar

E-mail: dradanur@yahoo.com

ORCID ID: 0000-0002-8291-1515

6. Selma EROĞLU, Assoc. Prof.

Department of Physical Medicine and Rehabilitation, Afyonkarahisar Health Sciences University Hospital, Afyonkarahisar

E-mail: seroglu79@gmail.com

ORCID ID: 0000-0002-3600-5482

7. Sevda ADAR, Asst. Prof.

Department of Physical Medicine and Rehabilitation, Afyonkarahisar Health Sciences University Hospital, Afyonkarahisar

E-mail: drsevdaadar@gmail.com

ORCID ID: 0000-0003-4294-6761

Corresponding Author: Songül İNCE, MD, Physiatrist

E-mail: songulince07@gmail.com

Department of Physical Medicine and Rehabilitation, Dinar State Hospital, Afyonkarahisar, Turkey

Telephone: +90 0553 426 73 85

ORCID: 0000-0002-5006-6409

ClinicalTrials.gov Identifier: NCT04734977.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

The manuscript is original, has not been previously published and has not been/will not be submitted for publication elsewhere while under consideration.

We accept full responsibility for the accuracy of all content, including findings, citations, quotations, and references contained within the manuscript.

The manuscripts final version has been seen and approved by all the authors.

All authors contributed to the revision and approval of the manuscript.

All authors have no conflicts of interest.

All authors have no funding or grants or equipment provided for the manuscript from any source or financial benefits.

Ethics Approval: All procedures performed in this study were in accordance with the ethical standards of the institutional and with the Declaration of the World Medical Association. Informed consent was obtained from all individual participants included in the study.

Acknowledgments: None.

The manuscript has not been presented in any form previously.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

ABSTRACT

Objective: The purpose of this study was to research the clinical effectiveness of high-intensity laser therapy (HILT) combined with exercise (EX) on pain, quality of life, and disability in patients with cervical radiculopathy (CR) and compared it with that of placebo (PL) and EX alone.

Design: Ninety participants with CR were randomized into three groups: HILT + EX (n = 30), PL + EX (n = 30), and EX only (n = 30). Pain, cervical range of motion (ROM), disability, and quality of life (SF-36 short form) were assessed at baseline and weeks 4 and 12.

Results: The mean age of the patients (66.7% female) was 48.9 ± 9.3 years. Pain intensity in the arm and neck, neuropathic and radicular pain levels, disability, and several parameters of SF-36 showed an improvement in the short and medium-term in all three groups. These improvements were greater in the HILT + EX group than in the other two groups.

Conclusion: HILT + EX was much more effective in improving medium-term radicular pain, quality of life, and functionality in patients with CR. Thus, HILT should be considered for the management of CR.

Keywords: High-intensity laser, Neck pain, Radiculopathy, Cervical

What is known?

- Compression-related neuroinflammation of the cervical spinal nerves and roots is the main problem in CR.

- Recent clinical and experimental studies contain evidence that lasers can enhance neuronal regenerative processes.

What is new?

- HILT reduced radicular pain and increased compliance with therapeutic exercise, improving functionality and quality of life.

- Coadministration of HILT with exercise can be used as an effective treatment for patients with chronic CR symptoms.

INTRODUCTION

Cervical radiculopathy (CR) is a disease process that involves inflammation in the cervical spinal roots.[1] It is a disabling disease with major negative effects on mental and physical functionality and social participation.[2,3] CR has an annual incidence of 83 cases per 100,000 people, and its prevalence increases in the fifth decade of life.[3]

CR is most commonly caused by cervical spondylosis and disc herniation; less common causes are trauma, tumors, synovial cysts, meningeal cysts, dural arteriovenous fistulas, and tortuous vertebral arteries. According to previous research, 97–99% of patients with CR experience arm pain, and 56–80% experience neck pain.[1]

Radicular pain in CR is a mixture of nociceptive and neuropathic pain, and the neuropathic component is related to the disease burden.[3] Several conservative treatments are available to treat CR: immobilization, collars, laser therapy, physical therapy, cervical traction, anti-inflammatory drugs, and epidural steroid injections.[4,5] The efficacy of individual treatments is controversial; a multimodal approach is recommended because it is more effective. However, little high-quality evidence supports the use of conservative treatment.[5]

Laser therapy is a non-invasive and painless method that has been effectively used to reduce pain in neuropathic diseases, such as trigeminal neuralgia, neuropathy, sciatic pain, and herpes zoster.[6,7] Laser therapy has both local and systemic effects that can improve nerve regeneration.[4,8] Tissue stimulation, the main mechanism of action of laser (photobiostimulation), affects the vascular structure, interstitial tissue, cells, and immune system.[9] The advantages of laser therapy are attributable to its analgesic, anti-edema, and

anti-inflammatory mechanisms.[10] Moreover, recent clinical and experimental studies have provided evidence that lasers can enhance neuronal regeneration.[11] High-intensity laser therapy (HILT) is an innovative, painless treatment; it is superior to low-intensity laser therapy because the energy transfer is more intense and it can impact a larger and deeper tissue domain. Therefore, some disease groups can be treated more effectively with HILT than with other laser types.[8,9]

Previous studies have demonstrated the efficacy of laser therapy for neuropathic pain, but evidence of its efficacy in CR with a high neuropathic pain burden is insufficient. This is the first study to investigate the effects of HILT with those of placebo on radicular symptoms, neuropathic pain, disability, and quality of life in patients with CR.

METHODS

Ethics approval

Participants were given information about the stages of the study process, and their written consent for participation was asked. This study was approved by the local ethics board of the university (Approval Number: 2020/529). All procedures were performed appropriately with the institution's ethical standards and with the 1964 Helsinki declaration and its later amendments. The present study was approved by the research ethics committee of the institution where this study was conducted, following the World Medical Association Declaration. This study complies with all CONSORT guidelines and reports the needful information accordingly (see Supplementary Checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/C56, and Supplemental Digital Content 2, http://links.lww.com/PHM/C57).

Participants

This study was a prospective, randomized, placebo-controlled trial to test the efficiency of HILT in people with CR. Ninety patients who presented at our outpatient clinic with unilateral arm and/or neck pain and were diagnosed with CR after clinical assessment were enrolled. The patients were evaluated three times (baseline: T0, week 4: T1, and week 12: T2) by an investigator who was blinded to the treatment groups. The following parameters were assessed: cervical joint range of motion (ROM), pain intensity in the neck and arms, neuropathic pain and symptom levels, and the effect of radiculopathy on disability and quality of life.

The inclusion criteria were as follows: an age of 20–65 years; a history of arm pain and/or neck pain for over 1 month; and clinical features of radicular involvement with a dermatomal and/or myotomal distribution and/or decreased reflexes in the upper extremities. Cervical MRI was performed on all patients whose history and physical examination indicated CR. Patients whose cervical MRI revealed disc herniation (foraminal stenosis, protrusion, or extrusion) resulting in pressure on the cervical spinal nerve/root were included. Electromyography (EMG) was applied to the patients in terms of chronicity, localization, the severity of the lesion, and other differential diagnoses (such as plexopathy and TOS).

Patients were excluded if they had received regional injection treatment in the past month; had previous surgery on or infection of the cervical spine; presented with entrapment neuropathies in the upper extremities, cervical myelopathy, malignancy, pregnancy, or shoulder or elbow pathologies; had been diagnosed with rheumatic, neurological, or demyelinating diseases; or did not agree to participate. In addition, the use of medical treatments (analgesic, anti-inflammatory, and neuropathic pain drugs) was prohibited during

the study. None of the enrolled patients had been treated with any physical modality (TENS, traction, etc.) in the cervical region in the past month.

Randomization

Patients were randomly distributed into three groups: HILT + exercise (EX) (n = 30); PL + EX (n = 30); and only EX (n = 30). Each patient was assigned an identification number, and the numbers were randomized with Randomizer.org software. Figure 1 provides a flowchart of the study process. The patients did not know which group they were assigned to, which treatment they received, or whether they received real or sham HILT. The same physiotherapist administered all laser treatments, and the physiotherapist who provided exercise therapy was blinded to which treatment group the patients were in. Furthermore, the investigator who evaluated the patients at baseline and in the follow-ups did not know which treatment group the patients were in.

Interventions

Patients received pulse neodymium-doped yttrium aluminum garnet (Nd: YAG) laser therapy (HIRO 3. 0; ASA laser, Arcugnano, Italy). The appliance[10] has a pulse emission (1064 nm), high-level fluency or energy intensity (360–1.780 mJ/cm), a short period (120–150 μs), a very high peak power (3 kW), a mean power of 10.5 W, a low frequency (10–40 Hz), a probe diameter of 5 mm, and a spot size of 0.2 cm^2. HILT was applied to each patient in a sitting position with the probe perpendicular to the treated area. Scanning was performed circularly, transversely, and longitudinally from the C4 to T4 posterior neck in the paraspinal region; the interscapular domain; and the scalene, trapezius, and rhomboid muscles. Each session included three stages.

In the first stage, the manual scanning of the bilateral paravertebral region; the interscapular area; and the scalene, trapezius, and rhomboid muscles was performed rapidly. This consisted of three substages: 360 mJ/cm^2 (208 J), 410 mJ/cm^2 (208 J), and 510 mJ/cm^2 (209 J), for a total of 625 J (1250 J bilaterally). In the second stage, 33 J of energy was given to each of four tender/trigger points (two points on each side); a total of 132 J was delivered in this stage (the trigger point inactivation stage). This stage had four substages for 6 seconds each: 360 mJ/cm^2 (6.3 J), 510 mJ/cm^2 (9 J), 610 mJ/cm^2 (10.1 J), and 360 mJ/cm^2 (7.8 J). The first point was between C7 and the acromion, and the second point was in the interscapular region. The third stage was similar to the first stage, but it was implemented more slowly, and the total energy dose was 1250 J. One session lasted 20 minutes, and a total of 2632 J energy was applied during each session. HILT was performed for 20 sessions (five sessions a week for 4 weeks).

In the PL group, laser probe scanning was applied to the same areas as that applied in the HILT procedure. After the device was turned on, PL was applied while the lights of the device were on, with no current flowing through the device. Placebo therapy was applied at the same frequency as HILT (five sessions a week for 4 weeks for a total of 20 sessions; one session lasted 20 minutes). The same physiotherapist performed all laser treatments.

A total of 20 sessions (30 minutes each) of a therapeutic exercise program were provided to all three treatment groups by a trained physiotherapist. The sessions involved active and passive ROM exercises; cervical isometric and progressive (self-training with TheraBand) muscle-strengthening exercises; gentle stretching of the scalene, trapezius, rhomboid, levator scapulae, and pectoral muscles; and scapular stabilization exercises. The participants were asked to perform the exercises in three sets (with one set performed in the

hospital, supervised by a physiotherapist who was blinded to the treatment groups), with 10 repetitions in each set, three times a day; the participants performed five sessions a week for 4 weeks. The patients receive telephone calls once a week during the treatment program; the patients were asked to report their compliance with the exercises, their level of pain, and their use of analgesics, and they were provided with information to strengthen their understanding of the importance and benefits of exercise. The phone calls lasted 5–10 minutes on average, and all telephone calls were conducted by a blinded investigator.

Outcome measures

The outcome measures were performed 3 times; before treatment (T0), during treatment (T1: week 4), and at the end of the 12th treatment week (T2).

Primary Outcome Measure of the Study

Pain intensity assessment: In the neck and arm pain (at rest, movement, and night) intensity assessment, a 100-mm horizontal visual analog scale (VAS; 100, worst pain; 0, no pain) was used for all participants.[10]

Secondary Outcomes

Neuropathic pain assessment: The PainDETECT questionnaire (PD-Q) was used to establish neuropathic pain features in CR. A higher score indicates a worse result (minimum: 0, maximum: 38).[12]

Radicular pain assessment: The Cervical Radiculopathy Impact Scale (CRIS) is a scale that assesses symptoms and limitations in cervical radicular pain. It consists of 3 sub-parameters (symptoms, energy&posture, and activities&actions) and contains a total of 21

items. Each sub-parameter has a score scale from 0 to 100. A higher score indicates a worse result.[13]

Cervical range of motion assessment: Cervical ROM was measured with a universal goniometer according to fixed anatomical landmarks. All patients were seated in an upright position, and the cervical ROM measurements were made with reference to anatomical landmarks: the tragus for the sagittal plane (flexion and extension), the nostrils for the coronal plane (right and left lateral bending), and the vertex point on the head for the transverse plane (right and left rotation) as neutral 0º.[14]

Functional activity assessment: The Neck Disability Index (NDI) is frequently used to determine neck disability. It contains 10 items in total. Each item is evaluated on a scale of 0 to 5. The higher score indicates a worse result.[2]

Health-related quality of life assessment: The 36-item Short Form Health Survey (SF-36) is widely used to evaluate the quality of life. The scale contains 36 items of 7 subgroups. Each subgroup has a score between 0 and 100. A higher score means a better outcome.[10]

Power analysis

The sample size was calculated with G*power 3.1.9.4 software (Germany). The following combination was used for sample calculation: a priori repeated measures analysis of variance (ANOVA) power analysis (between factors), an alpha level of 0.05, and a power (1-β) of 95% with three groups and three measurements. The main variable utilized for sample size calculation was neck and arm pain intensity (visual analog scale (VAS) scores). The effect size was based on Fritz et al.'s study.[15] The required sample size was estimated at

25 participants in each group. However, considering the possible loss during follow-up, each group was planned to have 30 participants.

Statistical analysis

Statistical analysis used SPSS software, version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive data were identified with mean and standard deviation (SD) for each continuous variable, and the frequency and number were used for each categorical variable. The Pearson chi-square test was utilized when conditions were provided to compare categorical variables; the Monte Carlo chi-square test was used when the conditions were not provided. The Shapiro–Wilk test was used to analyze a normal distribution of data ($p > 0.05$). One-way ANOVA was used for normally distributed data in between-group comparisons (rotation and lateral flexion ROM measurements, SF-36 parameters with physical function and vitality, NDI level, all CRIS sub-parameters); the Tukey test was used as post hoc analysis. Kruskal-Wallis test was used for non-normally distributed data in between-group comparisons (VAS scores, degrees of flexion and extension, sub-parameters of SF-36 parameters except physical function and vitality, PD-Q); the Dunn test was used as post hoc analysis.

The Friedman test was used for non-normally distributed data to compare repeated measurements within each group; the Wilcoxon signed-rank test with Bonferroni correction (a : 0,016) was used for pairwise comparisons when a significant difference existed between the 3 measurements. Repeated-measures ANOVA was used for normally distributed data. The least significant difference test (LSD) was used to determine the group that created the difference as a result of the ANOVA in repeated-measurement schemes. The outcomes were assessed with a 95% confidence interval, and statistical significance was set as $p<0.05$.

RESULTS

A total of 90 patients completed the study. The patients had a mean (SD) age of 48.9±9.3 years; 60 (66.7%) of them were women, and 30 (33.3%) were men. No notable difference existed between the groups in terms of demographic features before treatment (Table 1). However, differences were found in cervical flexion ROM measurement, PD-Q score, and some SF-36 sub-parameters among the pretreatment measurements (Table 2, 3 and 4).

Tables 2, 3, and 4 show the change over time in outcome measures between treatment groups. Pain intensity in the arm and neck (VAS), neuropathic (PD-Q) and radicular pain levels (CRIS), and neck functional disability level (NDI) showed a significant improvement in both the short and medium term in all 3 groups ($p<0.05$). These improvements were remarkably higher in the HILT group in the short and medium term ($p<0.05$; Table 2 and 3).

In the HILT and PL groups, a significant recovery occurred in the cervical ROM in the sagittal, coronal, and transverse planes in the short and medium term ($p<0.05$; Figs. 2, 3 and 4). In the EX-only group, a considerable recovery was detected in the measurement of cervical right and left rotation in the short term, as well as extension and left rotation in the medium term ($p<0.05$). HILT + EX showed remarkable superiority over the other groups in the medium term in degrees of extension ($p=0.005$), right rotation ($p=0.013$), and right lateral flexion ($p=0.000$; Table 3).

In both the short and medium term, all sub-parameters of the quality of life scale improved in the HILT and PL groups. The emotional role limitation, social functionality, and bodily pain sub-parameters showed significant improvement in the EX-only group ($p<0.05$).

The HILT + EX group showed a remarkable improvement in all SF-36 sub-parameters compared to the other 2 groups ($p<0.05$; Table 4).

No adverse effects were established with HILT, placebo therapy, or exercise therapy throughout the treatment and follow-up.

DISCUSSION

In patients with CR, exercise therapy combined with HILT significantly improved radicular pain, functional disability, and quality of life compared with exercise alone and placebo plus exercise. Therefore, we concluded that HILT reduces the inflammation of neural structures in patients with CR, regulates the release of neuromodulatory markers, and prevents conduction blockage. These effects reduce radicular pain, increase compliance with therapeutic exercise, and improve functionality and quality of life.

The main pathomechanism of CR is neural inflammation rather than mechanical compression. Ischemia and neuron damage due to compression lead to a decrease in axonal conduction velocity and neuroinflammation, which causes pain.[4] Even without mechanical compression, substances produced by a herniated nucleus pulposus can cause neural inflammation and structural nerve root abnormalities, such as chronic fibrosis.[16] Neuroinflammation involves an increase in inflammatory mediators and vascular permeability, leukocyte infiltration, and glial cell activation. Specifically, nerve damage causes substantial glial cell activation in the spinal cord.[17] Permanent glial cell activation is responsible for sustained neuroinflammation and continued neuropathic pain.[17,18] When the mixed pain pattern in patients with CR is not adequately controlled, the neuropathic pain

component becomes dominant, leading to increased disability and a deterioration in quality of life.[3]

In diseases with neuropathic pain components, nonpharmacological methods are preferred for pain management because of the adverse effects of medical treatments.[19] One of these methods is laser therapy, and studies have shown that this method improves neuropathic pain control.[7,20,21] Laser therapy modulates microglial activity and neuronal energy metabolism, regulates blood flow, and reduces the inflammatory response and oxidant activity; thus, it has a neuroprotective effect.[20,22] According to the results of a systematic review evaluating the effect of laser therapy on the peripheral nerves, this method can reduce acute pain by acting directly on peripheral nociceptors. In patients with chronic pain, laser application can cause changes at the spinal cord level, providing long-term pain reduction.[21] Many preclinical animal studies have shown that the application of laser therapy to spinal cord injuries reduces the expression of glycogen synthase kinase-3 beta (GSK3-β), which inhibits the regrowth of axons and causes neuropathic pain; in addition, it provides functional repair.[23]

Because HILT provides more intense energy to deeper tissues than low-intensity laser therapy, its ability to repair damaged tissues and eliminate painful stimuli is more obvious.[8] A comprehensive meta-analysis reported that spinal disorders can be effectively treated with a high-intensity 1064 nm laser.[24] In a study on patients with chronic neck pain, Alayat et al. determined that HILT + EX increased the cervical ROM and significantly reduced VAS and the neck disability index (NDI) compared with PL + EX.[25] In another study on patients with chronic low back pain, HILT + EX was superior to HILT alone and PL + EX regarding pain and functionality.[26] Furthermore, a study involving 174 patients with cervical spondylosis

with radicular symptoms reported a significant decrease in medium-term VAS scores in the HILT group compared with the traction group.[27] The present study evaluated the efficacy of HILT treatment with both the VAS and the PainDETECT questionnaire; we observed a significant improvement in both assessment criteria in the short and medium term. We postulate that HILT achieved this positive effect by reducing neuronal inflammation.

Increasing evidence suggests that HILT improves the quality of life in patients with spinal radicular syndrome.[28] Three recent studies (two examining the cervical region and one examining the lumbar region) comparing HILT with sham laser therapy (both combined with exercise) found that HILT improved quality of life scores (assessed by the SF-36) more than sham therapy.[10,25,26] The results of the current study revealed that HILT + EX was superior to both placebo and exercise alone in all subparameters of the SF-36. These results are compatible with those found in the literature.

Exercise is a crucial intervention for patients with CR. Stolzman et al. established that exercise could provide conditional modulation and reduction of pain via the activation of inhibitory pathways.[29] In a randomized controlled trial involving 75 patients with CR, Halvorsen et al. suggested that 14 weeks of neck-specific training and physical activity aimed at improving sensory and motor function could reduce the intensity of neuropathic pain.[30] The results of our study support the evidence that exercise can reduce pain levels and neck disability and improve functionality in patients with CR.

Study limitations

The main limitations of this study are that it had a small sample size, lacked long-term (>3 months up to 1 year) follow-up results, was performed at a single center, did not use

an algometer-like device to gather quantitative data to evaluate pain, and did not evaluate serum biomarker levels to observe the changes in radicular pain in response to treatment. Another limitation of the study it did not include an older age group. Older patients likely have a significantly higher disease burden than younger adults. Older patients (over 65 years) were not included in this study because of their higher rate of degenerative findings, economic constraints, lack of insurance, and communication issues (e.g., hearing difficulties interfering with telephone interviews). Finally, the physiotherapist who provided the HILT/PL intervention was not blinded to the treatment.

Conclusions

Co-administration of HILT with exercise was more effective than placebo or exercise alone in reducing radicular pain and improving functionality and quality of life in patients with CR. These effects persisted in the medium term.

Conflict of interest: The authors declare that they have no conflict of interest.

Funding: No funding was received for this study.

Availability of data, code, and other materials: All data are available upon reasonable request from the corresponding author.

References

1. Kang K-C, Lee HS, Lee J-H. Cervical radiculopathy focus on characteristics and differential diagnosis. *Asian Spine J*. 2020;14(6):921.
2. Young IA, Cleland JA, Michener LA, Brown C. Reliability, construct validity, and responsiveness of the neck disability index, patient-specific functional scale, and numeric pain rating scale in patients with cervical radiculopathy. *Am J Phys Med Rehabil*. 2010;89(10):831-839.
3. Tampin B, Slater H, Briffa NK. Neuropathic pain components are common in patients with painful cervical radiculopathy, but not in patients with nonspecific neck-arm pain. *Clin J Pain*. 2013;29(10):846-856.
4. Konstantinovic LM, Cutovic MR, Milovanovic AN, et al. Low-level laser therapy for acute neck pain with radiculopathy: A double-blind placebo-controlled randomized study. *Pain Med*. 2010;11(8):1169-1178.
5. Eubanks JD. Cervical radiculopathy: Nonoperative management of neck pain and radicular symptoms. *Am Fam Physician*. 2010;81(1):33-40.
6. Alayat MSM, Elsodany AM, El Fiky AAR. Efficacy of high and low level laser therapy in the treatment of Bell's palsy: A randomized double blind placebo-controlled trial. *Lasers Med Sci*. 2014;29(1):335-342.
7. Akyuz G, Kenis O. Physical therapy modalities and rehabilitation techniques in the management of neuropathic pain. *Am J Phys Med Rehabil*. 2014;93(3):253-259.
8. Ordahan B, Karahan AY, Kaydok E. The effect of high-intensity versus low-level laser therapy in the management of plantar fasciitis: A randomized clinical trial. *Lasers Med Sci*. 2018;33(6):1363-1369.
9. Boyraz İ, Yıldız A. Laser types and using of high intensity laser. *J Contemp Med*. 2016;6:104-109.

10. Dundar U, Turkmen U, Toktas H, Solak O, Ulasli AM. Effect of high-intensity laser therapy in the management of myofascial pain syndrome of the trapezius: A double-blind, placebo-controlled study. *Lasers Med Sci*. 2015;30(1):325-332.

11. Rochkind S, Geuna S, Shainberg A. Chapter 25: Phototherapy in peripheral nerve injury: effects on muscle preservation and nerve regeneration. *Int Rev Neurobiol*. 2009;87: 445-464.

12. Epping R, Verhagen AP, Hoebink EA, Rooker S, Scholten-Peeters GGM. The diagnostic accuracy and test-retest reliability of the Dutch PainDETECT and the DN4 screening tools for neuropathic pain in patients with suspected cervical or lumbar radiculopathy. *Musculoskelet Sci Pract*. 2017;30:72-79.

13. Gärtner FR, Marinus J, van den Hout WB, Vleggeert-Lankamp C, Stiggelbout AM. The Cervical Radiculopathy Impact Scale: Development and evaluation of a new functional outcome measure for cervical radicular syndrome. *Disabil Rehabil*. 2020;42(13):1894-1905.

14. Sukari AAA, Singh S, Bohari MH, Idris Z, Ghani ARI, Abdullah JM. Examining the Range of Motion of the Cervical Spine: Utilising Different Bedside Instruments. *Malays J Med Sci*. 2021;28(2):100.

15. Fritz JM, Thackeray A, Brennan GP, Childs JD. Exercise only, exercise with mechanical traction, or exercise with over-door traction for patients with cervical radiculopathy, with or without consideration of status on a previously described subgrouping rule: A randomized clinical trial. *J Orthop Sports Phys Ther*. 2014;44(2):45-57.

16. Kim E, Yoon JS, Kang HJ. Ultrasonographic cross-sectional area of spinal nerve roots in cervical radiculopathy: A pilot study. *Am J Phys Med Rehabil*. 2015;94(2):159-164.

17. Matsuda M, Huh Y, Ji RR. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. *J Anesth*. 2018;33(1):131-139.

18. Tsuda M, Shigemoto-Mogami Y, Koizumi S, et al. P2X4 receptors induced in spinal microglia gate tactile allodynia after nerve injury. *Nature*. 2003;424(6950):778-783.

19. Moisset X, Lefaucheur JP. Non pharmacological treatment for neuropathic pain: Invasive and non-invasive cortical stimulation. *Rev Neurol (Paris)*. 2019;175(1-2):51-58.

20. De Andrade ALM, Bossini PS, Parizotto NA. Use of low level laser therapy to control neuropathic pain: A systematic review. *J Photochem Photobiol B Biol*. 2016;164:36-42.

21. Chow R, Armati P, Laakso EL, Bjordal JM, Baxter GD. Inhibitory effects of laser irradiation on peripheral mammalian nerves and relevance to analgesic effects: A systematic review. *Photomed Laser Surg*. 2011;29(6):365-381.

22. Vogel DDS, Ortiz-Villatoro NN, Araújo NS, et al. Transcranial low-level laser therapy in an in vivo model of stroke: Relevance to the brain infarct, microglia activation and neuroinflammation. *J Biophotonics*. 2021;14(6): e202000500.

23. Ramezani F, Neshasteh-Riz A, Ghadaksaz A, Fazeli SM, Janzadeh A, Hamblin MR. Mechanistic aspects of photobiomodulation therapy in the nervous system. *Lasers Med Sci*. 2021;37(1):11-18.

24. Penberthy WT, Vorwaller CE. Utilization of the 1064 nm wavelength in photobiomodulation: A systematic review and meta-analysis. *J Lasers Med Sci*. 2021;12(1):86.

25. Alayat MSM, Mohamed AA, Helal OF, Khaled OA. Efficacy of high-intensity laser therapy in the treatment of chronic neck pain: A randomized double-blind placebo-control trial. *Lasers Med Sci*. 2016;31(4):687-694.

26. Alayat MSM, Atya AM, Ali MME, Shosha TM. Long-term effect of high-intensity laser therapy in the treatment of patients with chronic low back pain: A randomized blinded placebo-controlled trial. *Lasers Med Sci*. 2014;29(3):1065-1073.

27. Haładaj R, Pingot M, Topol M. The effectiveness of cervical spondylosis therapy with saunders traction device and high-intensity laser therapy: A randomized controlled trial. *Med Sci Monit*. 2017;23:335.

28. Alayat M, Alshehri M. High intensity laser therapy for treatment of spinal disorders. *Arch Phys Med Rehabil*. 2019;100(10):e151.

29. Stolzman S, Bement MH. Does exercise decrease pain via conditioned pain modulation in adolescents? *Pediatr Phys Ther*. 2016;28(4):470-473.

30. Halvorsen M, Falla D, Gizzi L, Harms-Ringdahl K, Peolsson A, Dedering Å. Short- and long-term effects of exercise on neck muscle function in cervical radiculopathy: A randomized clinical trial. *J Rehabil Med*. 2016;48(8):696-704.

Figure legends

Figure 1 Flowchart of the study

Figure 2 Change over time between groups in cervical flexion/extension

Figure 3 Change over time between groups in cervical right/left lateral bending

Figure 4 Change over time between groups in cervical right/left rotation.

Table legends

Table 1: Demographic features and baseline values for evaluation parameters of each 3 groups.

Table 2: Change over time in VAS, PD-Q, CRIS between treatment groups.

Table 3: Change over time in cervical active ROM and NDI between treatment groups.

Table 4: Change over time in SF-36 sub-parameters between treatment groups.

Figure 1

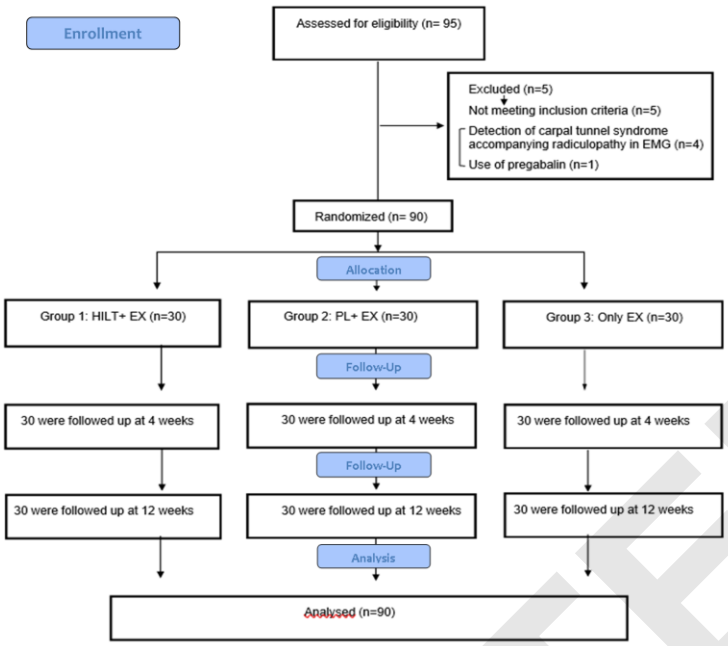

Figure 2

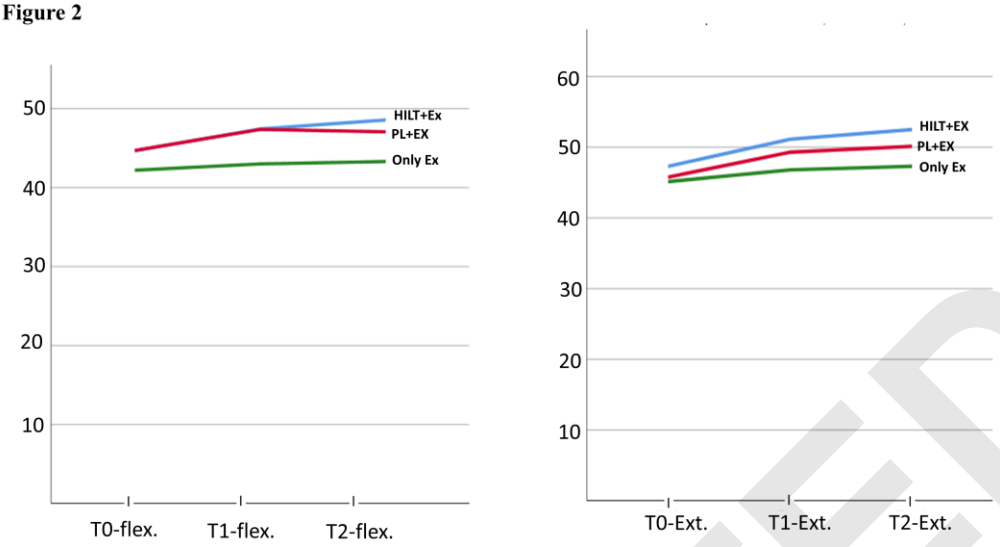

Figure 3

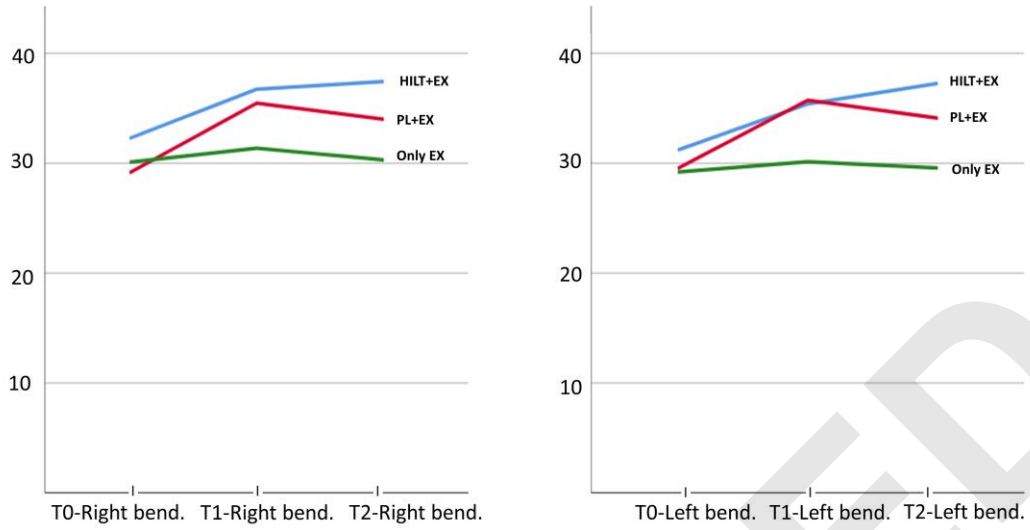

Figure 4

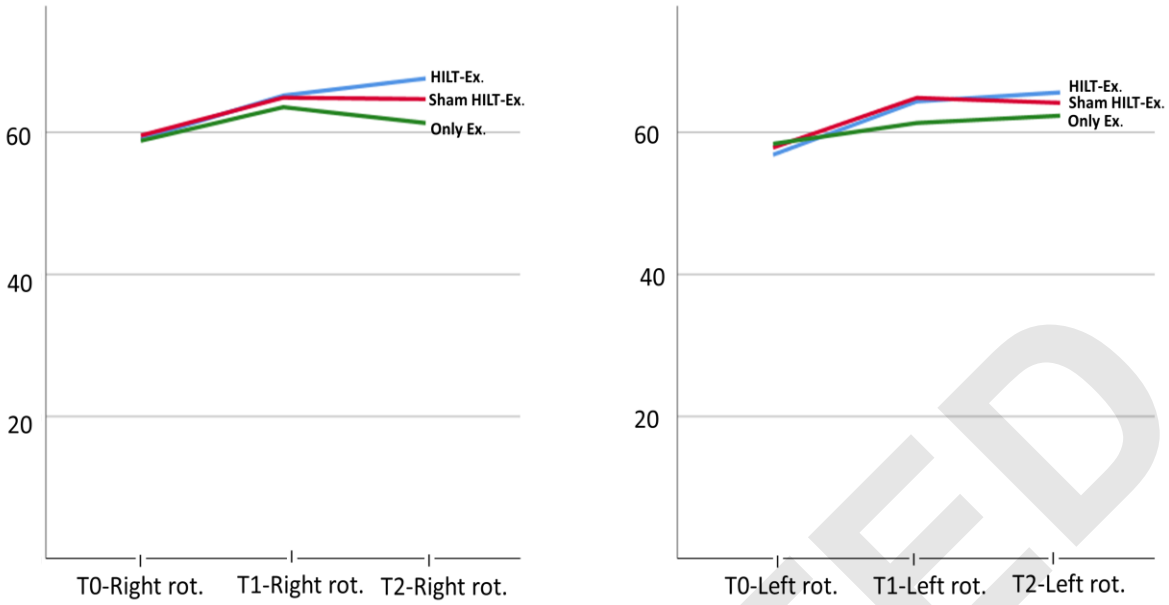

Table 1: Demographic and clinical features of each three groups.

	HILT+EX(n=30) (mean±SD)	PL+EX(n=30) (mean±SD)	Only EX(n=30) (mean±SD)	P
Age,years	47,1±10,3	49,1±7,3	50,4±10,2	0,395
Gender				
Female	17(%56,7)	22(%73,3)	21(%70)	0,350
Male	13(%43,3)	8(%26,7)	9(%30)	
Dominant side				
Right	26(%86,7)	26(%86,7)	27(%90)	0,902
Left	4(%13,3)	4(%13,3)	3(%10)	
Affected side				
Dominant	17(%56,7)	14(%46,7)	18(%60)	0,646
Non-dominant	13(%43,3)	16(%53,3)	12(%40)	
Duration of symptoms				
1-3 months	13(%43,3)	15(%50)	8(%26,7)	
3-6 months	4(%13,3)	5(%16,7)	8(%26,7)	0,355
>6 months	13(%43,3)	10(%33,3)	14(%46,7)	
Cervical MRI				
Disc protrusion	13(%43,3)	11(%36,7)	8(%26,7)	
Disc extrusion	0(%0)	0(%0)	1(%3,3)	0,472
Foraminal stenosis	17(%56,7)	19(%63,3)	21(%70)	
Cervical MRI, total affected root level (n)				
C4/C5/C6/C7/C8-T1	5/15/30/21/2	7/11/28/25/1	11/18/27/25/5	0,124

EMG consistent findings				
Yes	17(%56,7)	14(%46,7)	16(%53,3)	0,623
No	13(%43,3)	16(%53,3)	14(%46,7)	
EMG, total affected root level (n)				
no/C5/C6/C7/C8/T1	13/3/5/10/8/7	16/4/6/7/3/2	14/2/7/9/4/3	0,622
Paresthesias				
Yes	27(%90)	28 (%93,3)	27(%90)	0,872
No	3(%10)	2(%6,7)	3(%10)	
Weakness				
Yes	8(%26,7)	9(%30)	9(%30)	0,947
No	22(%73,3)	21(%70)	21(%70)	

EX exercise, *HILT* High-Intensity Laser Therapy, *PL* Placebo, *SD* Standart deviation, *MRI* Magnetic resonance imaging, *EMG* Conventional needle myography,

*P value is significant < 0.05, confidence interval %95

Table 2: Change over time in VAS, PD-Q, CRIS between treatment groups.

		HILT+EX(n=30) (mean±SD)		PL+EX(n=30) (mean±SD)		Only EX(n=30) (mean±SD)		P[2]
VAS (mm)								
AP at rest	T0	63,67	±16,29	66,33	±16,71	64,67	±12,24	0,771
	T1	19,00	±11,85^{Aa}	30,00	±13,90^{Bb}	42,33	±18,13^{C}	**0,000***
	T2	14,67	±11,67^{Aa}	35,33	±20,63^{B}	40,33	±23,56^{C}	**0,000***
	P[1]	**0,000***		**0,000***		**0,000***		
AP at movement	T0	78,67	±12,24	78,67	±16,34	81,67	±10,20	0,739
	T1	25,67	±14,31^{Aa}	39,67	±20,08^{Bb}	55,00	±19,78^{C}	**0,000***
	T2	21,33	±12,24^{Aa}	46,33	±23,12^{B}	50,67	±24,06^{C}	**0,000***
	P[1]	**0,000***		**0,000***		**0,000***		
AP at night	T0	76,33	±19,74	74,33	±17,94	77,33	±12,02	0,663
	T1	22,00	±16,06^{Aa}	34,00	±19,93^{Bb}	52,00	±19,37^{C}	**0,000***
	T2	16,00	±11,92^{Aa}	42,33	±23,44^{B}	46,00	±29,08^{C}	**0,000***
	P[1]	**0,000***		**0,000***		**0,000***		
NP at rest	T0	62,33	±17,75	68,00	±18,64	61,00	±11,55	0,207
	T1	23,00	±13,43^{Aa}	37,00	±18,78^{B}	39,67	±15,42^{C}	**0,000***
	T2	17,33	±12,58^{Aa}	38,00	±22,35^{B}	40,33	±22,20^{C}	**0,000***
	P[1]	**0,000***		**0,000***		**0,000***		
NP at movement	T0	74,33	±12,51	78,67	±16,34	77,00	±10,22	0,325
	T1	29,00	±12,69^{Aa}	44,00	±21,75^{B}	52,67	±18,93^{C}	**0,000***
	T2	26,00	±12,48^{Aa}	47,33	±24,49^{B}	54,67	±22,85^{C}	**0,000***
	P[1]	**0,000***		**0,000***		**0,000***		
NP at night	T0	72,67	±19,29	76,67	±17,88	72,00	±14,48	0,395

	T1	23,67	±14,74^{Aa}	38,67	±22,55^{B}	45,33	±18,89^{C}	**0,000***
	T2	19,67	±12,99^{Aa}	45,00	±24,74^{B}	46,00	±25,27^{C}	**0,000***
	P^{1}	**0,000***		**0,000***		**0,000***		
PD-Q	T0	16,60	±7,28	18,70	±6,62	13,93	±4,18	**0,030***
	T1	7,70	±3,91^{Aa}	10,90	±5,03^{B}	10,93	±3,90^{C}	**0,007***
	T2	5,43	±3,24^{Aa}	9,73	±5,19^{B}	10,63	±4,91^{C}	**0,000***
	P^{1}	**0,000***		**0,000***		**0,000***		
CRIS-S	T0	67,73	±12,26	68,54	±11,76	67,73	±8,75	0,948
	T1	28,18	±8,87^{Aa}	37,54	±14,20^{Bb}	50,42	±14,24^{C}	**0,000***
	T2	22,65	±8,36^{Aa}	40,71	±19,05^{Bb}	51,45	±18,70^{C}	**0,000***
	P^{1}	**0,000***		**0,000***		**0,000***		
CRIS-EP	T0	72,44	±18,43	76,62	±17,78	68,58	±17,23	0,223
	T1	29,53	±17,60^{Aa}	43,16	±18,81^{B}	53,12	±19,49^{C}	**0,000***
	T2	18,42	±12,65^{Aa}	40,25	±22,61^{B}	47,01	±22,75^{C}	**0,000***
	P^{1}	**0,000***		**0,000***		**0,000***		
CRIS-AA	T0	54,33	±28,16	55,66	±26,29	52,10	±17,50	0,787
	T1	17,47	±16,90^{Aa}	32,25	±20,70^{B}	37,22	±20,64^{C}	**0,001***
	T2	9,34	±11,12^{Aa}	27,00	±20,62^{B}	38,15	±25,66^{C}	**0,000***
	P^{1}	**0,000***		**0,000***		**0,000***		

EX exercise, *HILT* High-Intensity Laser Therapy, *PL* placebo, *SD* Standart deviation, *VAS* Visuel analog scala, *AP* Arm pain, *NP* Neck pain, *ROM* Range of motion, *PD-Q* Pain detect questionnare, *CRIS* Cervical radiculopathy impact scale, *CRIS-S* Symptoms, *CRIS-EP* Energy/postures, *CRIS-AA* Actions/activities. *P value is significant < 0.05, confidence interval %95. A, B, C and P^{1} show within-group comparison statistically significant (p<0.05); a, b, c and P^{2} show between-group comparison statistically significant (p<0.05).

Table 3: Change over time in cervical active ROM and NDI between treatment groups.

		HILT+EX (n=30) (mean±SD)		PL+EX (n=30) (mean±SD)		Only EX(n=30) (mean±SD)		P[2]
NDI	T0	23,90	±6,12	25,67	±7,63	22,80	±4,09	0,193
	T1	9,97	±4,65^{Aa}	15,30	±6,61^{B}	17,97	±5,52^{C}	**0,000***
	T2	8,03	±4,50^{Aa}	16,77	±7,70^{B}	17,60	±7,49^{C}	**0,000***
	P[1]	**0,000***		**0,000***		**0,000***		
ROM (°)								
Flexion	T0	44,67	±4,88	44,70	±5,07	42,20	±3,67	**0,011***
	T1	47,43	±4,21^{Aa}	47,37	±3,96^{Bb}	43,00	±3,84	**0,000***
	T2	48,57	±3,98^{Aa}	47,07	±4,65^{Bb}	43,30	±4,03	**0,000***
	P[1]	**0,000***		**0,000***		0,136		
Extension	T0	47,30	±7,78	45,77	±7,56	45,13	±6,12	0,089
	T1	51,13	±4,51^{Aa}	49,30	±5,84^{B}	46,80	±5,44	**0,003***
	T2	52,50	±4,49^{Aa}	50,13	±6,24^{B}	47,30	±6,62^{C}	**0,005***
	P[1]	**0,000***		**0,000***		**0,050***		
Right rotation	T0	59,03	±10,17	59,53	±6,38	58,80	±9,53	0,948
	T1	65,17	±8,94^{A}	64,87	±7,19^{B}	63,53	±9,47^{C}	0,736
	T2	67,57	±8,68^{Aa}	64,67	±8,66^{B}	61,30	±8,71	**0,013***
	P[1]	**0,000***		**0,000***		**0,002***		
Left rotation	T0	56,83	±10,92	57,83	±6,57	58,37	±6,76	0,770
	T1	64,33	±10,54^{A}	64,83	±8,43^{B}	61,30	±7,22^{C}	0,658
	T2	65,60	±8,36^{A}	64,13	±9,49^{B}	62,33	±7,10^{C}	0,269
	P[1]	**0,000***		**0,000***		**0,007***		

Right bending	T0	32,27	±6,93	29,13	±6,83	30,10	±6,54	0,191
	T1	36,73	±5,90^{Aa}	35,47	±6,65^{Bb}	31,37	±6,18	**0,003***
	T2	37,43	±6,42^{Aa}	34,00	±6,69^{B}	30,30	±5,69	**0,000***
	P^{1}	**0,000***		**0,000***		0,279		
Left bending	T0	31,20	±6,38	29,53	±8,04	29,20	±6,01	0,485
	T1	35,40	±6,16^{Aa}	35,73	±7,17^{Bb}	30,13	±5,76	**0,001***
	T2	37,27	±6,16^{Aa}	34,10	±7,39^{Bb}	29,57	±5,61	**0,000***
	P^{1}	**0,000***		**0,000***		0,542		

EX exercise, *HILT* High-Intensity Laser Therapy, *PL* placebo, *SD* Standart deviation, *ROM* Range of motion, *NDI* Neck disability index. *P value is significant < 0.05, confidence interval %95. A, B, C and P^{1} show within-group comparison statistically significant (p<0.05); a, b, c and P^{2} show between-group comparison statistically significant (p<0.05).

Table 4: Change over time in SF-36 sub-parameters between treatment groups.

		HILT+EX (n=30)	**PL+EX (n=30)**	**Only EX(n=30)**	
		(mean±SD)	**(mean±SD)**	**(mean±SD)**	P^2
SF-36					
PF	T0	42,67 ±18,18	38,67 ±23,41	41,17 ±11,87	0,698
	T1	54,83 ±17,29^{Aa}	44,00 ±21,83^{B}	45,00 ±12,25	**0,030***
	T2	58,67 ±18,10^{Aa}	46,00 ±22,30^{B}	45,83 ±15,54	**0,013***
	P^1	**0,000***	**0,000***	**0,038***	
RL	T0	21,67 ±25,20	6,67 ±13,02	18,33 ±21,71	**0,024***
	T1	67,50 ±30,90^{Aa}	40,00 ±31,89^{B}	25,00 ±33,48	**0,000***
	T2	81,67 ±24,51^{Aa}	50,00 ±34,11^{B}	35,00 ±29,07^{C}	**0,000***
	P^1	**0,000***	**0,000***	**0,021***	
RLEP	T0	37,74 ±32,41	14,43 ±24,24	37,74 ±29,96	**0,003***
	T1	86,65 ±25,68^{A}	72,20 ±30,44^{B}	72,21 ±36,19^{C}	0,117
	T2	93,32 ±16,16^{Aa}	72,20 ±29,15^{B}	81,10 ±29,93^{C}	**0,007***
	P^1	**0,000***	**0,000***	**0,000***	
V	T0	37,00 ±17,84	29,33 ±16,12	36,17 ±16,17	0,156
	T1	55,00 ±16,61^{Aa}	45,50 ±18,35^{B}	39,67 ±16,34	**0,003***
	T2	59,50 ±17,58^{Aa}	39,33 ±16,54^{B}	38,67 ±18,89	**0,000***
	P^1	**0,000***	**0,000***	**0,049***	
GMH	T0	46,27 ±16,13	40,93 ±14,47	48,27 ±12,60	0,134
	T1	63,87 ±13,47^{Aa}	55,87 ±14,76^{B}	53,33 ±11,71	**0,005***

	T2	66,60	±12,38^{Aa}	55,59	±14,16^{B}	51,73	±14,40	**0,000***
	P^{1}	**0,000***		**0,000***		0,070		
SF	T0	41,33	±21,87	32,50	±15,26	41,83	±14,93	0,102
	T1	72,50	±18,10^{Aa}	59,58	±18,48^{B}	52,08	±17,70^{C}	**0,000***
	T2	80,00	±18,74^{Aa}	59,75	±18,22^{B}	52,92	±22,19^{C}	**0,000***
	P^{1}	**0,000***		**0,000***		**0,008***		
BP	T0	27,00	±14,88	20,83	±10,14	29,17	±10,03	**0,028***
	T1	65,67	±14,25^{Aa}	54,33	±16,46^{Bb}	42,25	±13,68^{C}	**0,000***
	T2	71,58	±14,61^{Aa}	51,42	±19,02^{B}	41,75	±17,10^{C}	**0,000***
	P^{1}	**0,000***		**0,000***		**0,000***		
GH	T0	39,83	±10,95	39,17	±12,46	42,33	±9,07	0,584
	T1	52,67	±10,89^{Aa}	50,00	±12,59^{B}	43,50	±11,53	**0,023***
	T2	55,75	±11,05^{Aa}	46,67	±12,89^{B}	44,33	±16,07	**0,005***
	P^{1}	**0,000***		**0,001***		0,329		

EX exercise, *HILT* High-Intensity Laser Therapy, *PL* placebo, *SD* Standart deviation, *SF36* short-form 36 health survey, *PF* physical function, *RL* role limitations due to physical functioning, *BP* bodily pain, *GH* general health, *V* vitality, *SF* social functioning, *RLEP* role limitations due to emotional problems, *GMH* general mental health. P value is significant < 0.05, confidence interval %95. A, B, C and P^{1} show within-group comparison statistically significant (p<0.05); a, b, c and P^{2} show between-group comparison statistically significant (p<0.05).