

The Effectiveness of Adding High-Intensity Laser Therapy (HILT) to Physical Exercise in Reducing Pain, Improving Muscle Strength, and Enhancing Functional Ability in Patients with Knee Osteoarthritis: A Randomized Controlled Trial

Laksmana Rizki, Tirza Z Tamin, Fitri Anestherita,
Harrison Handoko

Department of Physical Medicine and Rehabilitation Cipto Mangunkusumo Hospital,
Universitas Indonesia, Jakarta, Indonesia

Abstract

Introduction: Osteoarthritis (OA) is a leading cause of disability worldwide, impacting patient's daily functional abilities as well as quality of life due to chronic pain associated with joint damage. High-Intensity Laser Therapy (HILT) has been proven effective in reducing pain and improving function in patients with knee OA. Despite its recognition as a safe and effective modality, standardized protocols for its use in knee OA are lacking. This study aims to evaluate the effectiveness of incorporating HILT in addition to physical exercise programs for patients with knee OA.

Methods: 30 patients with knee OA were randomized into 2 groups, HILT + physical exercise (intervention group), and physical exercise only (control group). Visual Analogue Scale (VAS), quadriceps and hamstring muscle strength using exercise testing, and functional ability using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire were measured and compared.

Result: Both groups displayed statistically significant improvement in pain, muscle strength, and functional ability by the end of the program (week 4) compared to the initial examination ($p < 0.05$). When compared, there was a significant difference in pain reduction and functional ability in favor of the intervention group ($p < 0.05$). However, there were no significant differences in quadriceps and hamstring muscle strength between the groups ($p = 0.148$ and $p = 0.345$, respectively).

Conclusion: In this study, it was shown that the combination of HILT and physical exercise was more effective in alleviating pain and enhancing functional ability in patients with knee OA compared to physical exercise alone.

Keywords: High-intensity laser therapy, Knee osteoarthritis, Pain, Muscle strength, Functional ability.

Efektivitas Penambahan Terapi Laser Intensitas Tinggi (High-Intensity Laser Therapy / HILT) terhadap Latihan Fisik dalam Mengurangi Nyeri, Meningkatkan Kekuatan Otot, dan Memperbaiki Kemampuan Fungsional pada Pasien dengan Osteoarthritis Lutut: Suatu Uji Acak Terkontrol

Laksmiana Rizki, Tirza Z Tamin, Fitri Anestherita, Harrison Handoko

Departemen Rehabilitasi Medik Rumah Sakit Cipto Mangunkusumo,
Universitas Indonesia, Jakarta, Indonesia

Abstrak

Pendahuluan: Osteoarthritis (OA) merupakan salah satu penyebab utama disabilitas di seluruh dunia, yang berdampak pada kemampuan fungsional serta kualitas hidup pasien akibat nyeri kronis yang berhubungan dengan kerusakan sendi. High-Intensity Laser Therapy (HILT) telah terbukti efektif dalam mengurangi nyeri dan meningkatkan fungsi pada pasien dengan OA lutut. Meskipun telah dikenal sebagai modalitas yang aman dan efektif, hingga kini belum terdapat protokol standar mengenai penggunaannya pada OA lutut. Penelitian ini bertujuan untuk mengevaluasi efektivitas penambahan HILT terhadap program latihan fisik terhadap pasien dengan OA lutut.

Metode: Sebanyak 30 pasien dengan OA lutut diacak ke dalam dua kelompok: kelompok intervensi (HILT + latihan fisik) dan kelompok kontrol (latihan fisik saja). Parameter yang diukur dan dibandingkan meliputi Visual Analogue Scale (VAS) untuk nyeri, kekuatan otot kuadrisep dan hamstring menggunakan uji latihan, dan kemampuan fungsional menggunakan kuesioner Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Hasil: Kedua kelompok menunjukkan perbaikan yang bermakna secara statistik dalam hal nyeri, kekuatan otot, dan kemampuan fungsional pada akhir program (minggu ke-4) dibandingkan dengan pemeriksaan awal ($p < 0,05$). Saat dibandingkan antar kelompok, terdapat perbedaan bermakna pada penurunan nyeri dan peningkatan kemampuan fungsional yang lebih besar pada kelompok intervensi ($p < 0,05$), namun tidak ditemukan perbedaan bermakna pada kekuatan otot kuadrisep dan hamstring sebelum dan setelah intervensi pada kedua kelompok (masing-masing $p = 0,148$ dan $p = 0,345$).

Kesimpulan: Studi ini menunjukkan bahwa kombinasi HILT dan latihan fisik lebih efektif dalam mengurangi nyeri dan meningkatkan kemampuan fungsional pada pasien dengan OA lutut dibandingkan latihan fisik saja.

Kata Kunci: High intensity laser therapy, Osteoarthritis lutut, Nyeri, Kekuatan otot, Kemampuan fungsional.

Introduction

Osteoarthritis is the most prevalent type of arthritis and a major contributor to long-term disability globally, affecting patients' daily functional abilities and quality of life due to chronic pain resulting from joint damage.^{1,2} In addition to the physical impact it has on patients, OA also negatively influences mental health, contributing to issues such as depression, sleep disturbance, as well as mood alterations.³ The pathogenesis of OA involves mechanical, cellular, as well as biomechanical factors causing inflammation and joint tissue degeneration. These damages cause changes within the joint structures such as cartilage,

subchondral bone, synovium and surrounding soft tissues.⁴

The International Classification of Functioning, Disability, and Health (ICF) acknowledges that structural and functional changes in patients suffering from OA result in various disabilities, particularly ambulation difficulties. Impairment contributes to a decline in functional capacity and hinders participation in daily activities, such as walking and performing routine tasks.⁵

The management of OA includes both surgical and conservative approaches, focusing on pain reduction and joint function improvement. Conservative management includes both pharmacological and non-phar-

macological approaches.^{6,7} Non-pharmacological approaches such as physical exercise have been shown to improve perfusion to joint cartilage, facilitating healing as well as symptom relief.^{8,9}

HILT is a new innovation in the non-pharmacological management of knee OA. HILT delivers focused laser energy to deep tissues, promoting pain relief, reducing inflammation and stimulating tissue repair. HILT has been shown to improve joint function as well as alleviate pain in patients with knee OA, especially when combined with physical therapy.¹⁰ HILT utilizes lasers to produce a monochromatic, coherent, and collimated beam at 1064 nm, typically employing Nd:YAG lasers. This helps penetrate deeper structures beneath the skin non-invasively such as subcutaneous tissues, muscles, tendons, and bones. Short application time and the ability to reach deep tissue provide additional benefits that might otherwise be unavailable in other management approaches. Once the laser has reached the deeper structures, energy from the laser is absorbed by mitochondrial protons, stimulating repair and positive physiologic responses.^{10,11}

HILT produces several therapeutic effects such as pain relief, reduction of inflammation, microcirculation improvements, biological processes stimulation, and muscle relaxation.¹² HILT is commonly indicated for managing pain, including osteoarthritis. However, it is not recommended for use near the orbits and eyes, in patients with tumours, pregnancy, or over body parts containing metal implants. When applied properly, HILT is regarded as a safe treatment with minimal risk of adverse effects. However, despite HILT being safe and effective, standardized protocols for its application in knee OA remain unclear.¹³ Variabilities in laser type, wavelength, power output, energy density, dosage, frequency, and application have caused disparity in study outcomes.

This study aims to assess the effectiveness of incorporating HILT into the management of pain for patients with knee OA compared to only physical exercise. Participants were randomly assigned to one of two groups: a control group, receiving only physical exercise, and an intervention group which received a combination of HILT and physical therapy. In this study, several parameters were measured to compare the outcome between the two groups: Pain evaluated with VAS, quadriceps and hamstring muscle strength using exercise testing, and functional ability evaluated with WOMAC.

Method

Population and Sample

The target population for this study are patients experiencing knee pain due to OA in Indonesia within the environment of Rumah Sakit Umum Pusat Nasional Cipto Mangunkusumo (RSCM) Hospital, Jakarta, Musculoskeletal Rehabilitation outpatient clinic from January-July 2023. Inclusion criteria were knee OA based on the American College of Rheumatology (ACR), Kellgren-Lawrence (KL) grade 1–3, aged 50–75 years old, leading a sedentary lifestyle, experiencing knee pain with a VAS score of 3–7, good cognitive function, and gave informed consent to participate in the study. Exclusion criteria for this study include: contraindications for HILT (tumors or cancer, pregnancy, areas with sensory deficits, metal implants, and fever), musculoskeletal disorders affecting the knee other than OA, a history of intra-articular knee injections within the past three months, and unstable cardiovascular or metabolic conditions. For randomization, 30 participants who met the inclusion criteria were allocated into two groups: HILT plus physical therapy or physical therapy alone. Participants were advised to reach out to specialist staff for any queries or assistance needed during the study. Participants were also given the option to withdraw from the study at any time.

Data Measurement

Participants received HILT using BTL-6000 High Intensity Laser device (wavelength: 1064 nm; power: 12 Watts) equipped with a 30 mm spacer probe. Subjects were positioned in supine positions with the affected knee flexed, while the laser probe was placed perpendicular to the treatment area. Patients and physiotherapists were given protective goggles to ensure retinal safety. The therapy was applied to both the medial and lateral sides of the knee. The HILT treatment protocol included 2 phases:

1. Analgesic Phase, this phase was performed using a spiral motion, starting at 5–7 cm away from the most painful area and gradually moving centripetally toward the pain zone in 3–4 spiral rotations. The probe was then held in position for 2–3 seconds. This process was repeated until the participants were accustomed to the pain. The program settings included L-7129, with a power output of 10 W, a frequency of 25 Hz, an energy density of

12 J/cm², for 2 minutes, and a total dose of 300 J.

2. Biostimulation Phase, this phase involves a scanning motion following the direction of muscle fibers. Thermal feedback from the subject was requested to prevent overheating. The scanning technique was repeated until the biostimulation phase of the therapy was completed. The program settings used were L-7130, with a power output of 5 W, continuous frequency, energy density of 120 J/cm², for 10 minutes, and a total dose of 3000 J.

Both treatment groups were provided with conservative care, which included education on knee OA covering topics such as weight management, exercise, and lifestyle changes. Physical exercise was given to both groups on the same day by a trained physician as the HILT treatment consisting of:

1. Stretching, before the exercise were performed targeting the quadriceps, hamstrings, and gastrocnemius muscles. Each stretching was held for 10 seconds and repeated three times on both legs.
2. Aerobic Training using a stationary bike, following the Astrand ergo cycle test to determine the appropriate intensity.¹⁴ The target was set at 60–70% of maximum heart rate depending on the patient's age. Exercise was conducted for 15 minutes for the first two weeks and 30 minutes for the subsequent two weeks.
3. Strength Training was done after assessment using an NK table to determine the 10-repetition maximum (10RM) and the training dose was established. Quadriceps and hamstring muscles were strengthened using the NK table, following the DeLorme method (50–75–100% of 10RM).¹⁵ Training doses were adjusted based on evaluations at the end of the second week.
4. Balance Training was done on a balance board after initial assessment using Timed Up and Go test. Sessions were conducted for 15 minutes during the first two weeks and 30 minutes during the subsequent two weeks.
5. The exercise protocol was discontinued if systolic blood pressure exceeded 200 mmHg or diastolic blood pressure exceeded 110 mmHg, or if there was a decrease in systolic blood pressure greater than 10 mmHg or in the absence of an increased heart rate when tested using a sphygmomanometer. Exercise will also be stopped if oxygen levels dropped below 90% on

peripheral pulse oxymeter, or if the participants reported symptoms like shortness of breath, chest discomfort, dizziness, nausea, pallor, or requested to stop the exercise.

The primary outcome was the pain score (assessed with VAS) before the trial and VAS score in subsequent weeks until the end of the trial. The secondary outcome included muscle strength at the beginning, second and fourth week of the trial as well as WOMAC scores before and after the trial at the fourth week.

Data Analysis

Descriptive analysis was performed on all data under study, including the normality distribution. If the data followed a normal distribution, Independent Samples T-test for comparing the means of the two independent groups would be conducted, and the results would be presented as means and standard deviations. If the data did not follow a normal distribution, the Mann-Whitney test would be used instead, and the results would be presented as medians along with the minimum and maximum values. A p-value of <0.05 was considered statistically significant, with a 95% confidence interval (CI). All analysis was conducted using IBM SPSS ver 25.

Result

A total of 46 participants were recruited for the study, 16 of which did not meet the eligible criteria for the study. The remaining 30 participants were randomly allocated to either intervention or control group as seen in Figure 1.

Table 1 shows the baseline characteristics of all study participants, the basic characteristics assessed in this study include age, gender, body mass index (BMI), education level, occupation, and the degree of knee OA according to KL.

The mean age of participants in both groups was similar, at 59.9 (± 5.2) years old in the intervention group and 58.8 (± 7.4) years old in the control group. The gender distribution in both groups were predominantly female, 80% in the intervention group and 100% in the control group. Most participants are obese, 66.7% in the intervention group and 73.3% in the control group. The highest level of education was predominantly low to middle (elementary school to high school), 80% for the intervention group and 53.3% for

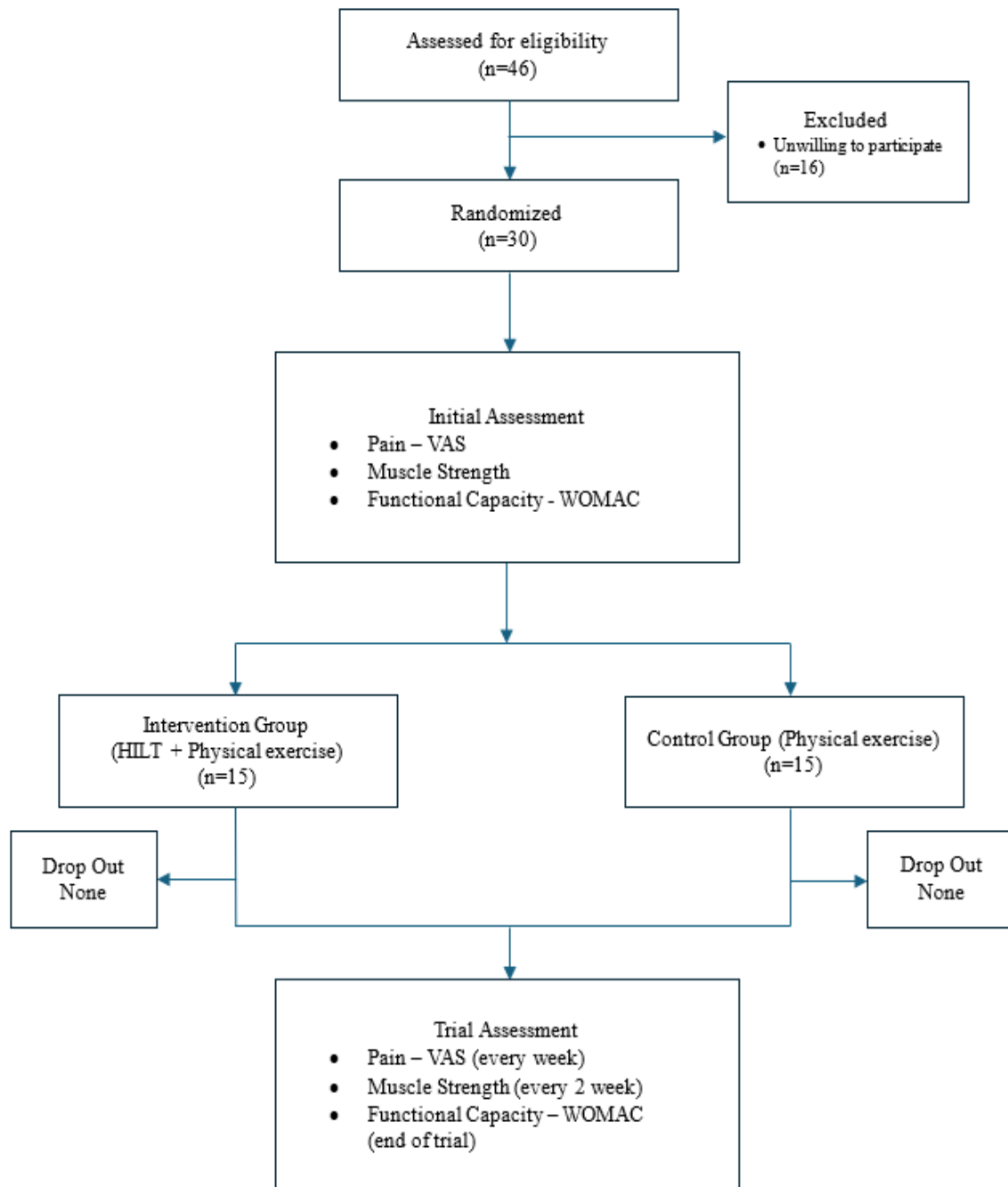


Figure 1. Consort Diagram of Protocol

the control group. Most participants in both groups were housewives or unemployed. Statistical analysis revealed there were no significant differences in the baseline characteristics between the two groups ($p > 0.05$). KL score for both groups varied with the intervention group predominantly being classified as KL 2 (53.3%), while the control group was mostly classified as KL 3 (60%). However, the difference was not statistically significant ($p > 0.05$). There were also no statistically significant difference in the initial outcome measured in both groups before treatment.

Pain score (VAS) was the primary outcome of this study. Overall, both groups showed a significant decline in VAS score from initial assessment as seen in Table 2 and Table 3 throughout the whole treatment period.

When the results from both groups were compared, a statistically significant difference in pain reduction was observed from the first to the fourth week at the end of the program ($p < 0.005$) as seen in Table 4 in favor of the intervention group.

The secondary outcome, muscle

Table 1. Baseline Demographic and Characteristics of Participants

Characteristics	Intervention Group (n=15)	Control Group (n=15)	P-value
Age (year)	59.93 ± 5.19	58.80 ± 7.42	0.63 ^a
Gender (%)			
Male	3 (20)	0 (0)	0.22 ^b
Female	12 (80)	15 (100)	
BMI (%)			
Non-Obese	5 (33.3)	4 (26.7)	1.00 ^c
Obese	10 (66.7)	11 (73.3)	
Education (%)			
Elementary-Highschool	12 (80)	8 (53.3)	0.12 ^c
Bachelor	3 (20)	7 (46.7)	
Occupation (%)			
Unemployed /Housewife	11 (73.3)	9 (60)	0.44 ^c
Employed	4 (26.7)	6 (40)	
KL OA Scale (%)			
KL 2	8 (53.3)	6 (40)	0.46 ^c
KL 3	7 (46.7)	9 (60)	
VAS	6 (4-7)	5 (4-7)	0.12 ^d
Muscle Strength (kg)			
Quadriceps	3 (1.5-7)	4 (0.5-10)	0.31 ^d
Hamstring	1.5 (0.5-4.5)	1.5 (0-5)	0.49 ^d
WOMAC			
Total	44 (30-79)	43 (28-64)	0.39 ^d
Pain	13 (10-18)	12 (8-16)	0.15 ^d
Stiffness	3 (0-7)	3 (2-4)	0.59 ^d
Physical Function	31 (19-57)	27 (18-46)	0.35 ^d

^aIndependent t-test; ^bFischer test; ^cChi-Square test; ^dMann-Whitney test
 BMI, body mass index; KL, Kellgren Lawrence; OA, osteoarthritis; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index;

Table 2. VAS Score Throughout Intervention (Intervention Group)

VAS	Median (Min-Max)	p-value
Pre-intervention	6 (4-7)	
Week 1	5 (3-7)	<0.001 *
Week 2	4 (3-6)	<0.001 *
Week 3	4 (2-5)	<0.001 *
Week 4	3 (2-5)	<0.001 *

Median VAS score were obtained from participants in intervention group every week following HILT and physical therapy. A *Wilcoxon Test was conducted to compare the results, a p-value of <0.05 is considered significant.

strength and functional capacity (WOMAC) was also compared between intervention and control group as seen in Table 5 and Table 6 although both groups displayed similar outcome.

As seen in Table 6, comparative analysis of functional ability between the intervention and control groups showed significant differences in the improvement of total WOMAC scores, particularly for pain and physical function components ($p < 0.001$). The reduction in total WOMAC scores was notably greater in the intervention group, with a decrease of 11 points more than the control group. Although, no significant changes were noted for joint stiffness between group ($p = 0.325$).

Discussion

The combination of HILT along with physical exercise has been shown to be more effective in reducing pain compared to physical exercise alone. This finding is also sup-

Table 3. VAS Score Throughout Intervention (Control Group)

VAS	Median (Min-Max)	p-value
Pre-intervention	5 (4-7)	
Week 1	5 (3-7)	0,025 *
Week 2	4 (2-6)	0,002 *
Week 3	4 (2-6)	0,001 *
Week 4	4 (2-5)	0,001 *

Median VAS score were obtained from participants in intervention group every week following HILT and physical therapy. A *Wilcoxon Test was conducted to compare the results, a p-value of <0.05 is considered significant.

Table 4. Comparison of VAS Pain Score

VAS	Intervention Group	Control Group	p-value
Delta Week 1	1 (0-2)	0 (0-1)	0.001 *
Delta Week 2	2 (1-3)	1 (0-2)	0.002 *
Delta Week 3	2 (2-3)	1 (0-3)	0.005 *
Delta Week 4	3 (2-4)	2 (0-3)	0.001 *

Median change in VAS score was compared from participants in intervention group and control group. A *Mann-Whitney Test was conducted to compare the results, a p-value of <0.05 is considered significant

ported by Angelova, et al¹⁶ that shows the effect of HILT therapy can last up to 3 months post treatment. HILT utilizes higher intensity and extended wavelengths (>1000 nm), allowing optimal energy levels to reach deep tissues, making it highly effective in relieving pain associated with musculoskeletal problems.¹⁷

The analgesic effects of HILT arises from two primary mechanisms. Firstly, it promotes the release of endogenous opioids, such as beta-endorphins and serotonin that bind to nociceptors and blocking pain signals from those receptors. Secondly, it disrupts pain signal transmission by lowering ATP production, reducing calcium influx to the dorsal root ganglion, inhibiting propagation of action potential for pain sensation. In this study we used BTL-6000 High Intensity Laser device which produces a monochromatic, coherent, and collimated beam at 1064 nm, typically employing Nd:YAG lasers, this involves delivering 12J/cm² to a 25 cm² area on the medial and lateral sides of the knee. Here, the laser stimulates large-diameter nerve fibers (A-beta fibers), which effectively “close the gate” at the spinal level, thereby inhibiting the transmission of pain signals from the periphery to the brain. In addition to pain perception modulation, the laser also demonstrates an anti-inflammatory

effect, by affecting key inflammatory mediators such as cyclooxygenase and lipoxygenase, therefore reducing the synthesis of prostaglandins and prostacyclin hence reducing inflammation. When applied at higher levels, the focus shifts toward tissue regeneration and functional recovery, where mitochondrial activity, ATP production, cell metabolism are increased, accelerating the repair of damaged joint structures.^{12,18}

In the context of knee OA, exercise remains a cornerstone of non-pharmacological therapy aimed at reducing pain and improving joint function. Weakened muscles, especially the quadriceps, increase the burden on the joint. Exercise strengthens these muscles, allowing them to absorb more shock and reduce mechanical stress on the worn cartilage. Apart from this, exercise has been shown to improve proprioception, coordination, and motor control, allowing patients to perform movements more efficiently with less joint irritation. Importantly, exercise stimulates the release of anti-inflammatory myokines such as IL-6, IL-10, and BDNF, which reduce low-grade inflammation commonly seen in OA.¹⁹ Currently, there are limited studies that show

Table 5. Comparison of Muscle Strength

Muscle Strength (Kg)	Intervention Group	Control Group	p-value
Quadriceps			
Delta Week 2	1 (0-1.5)	0.5 (0-1)	0.126 *
Delta Week 4	1 (0-3.5)	0.5 (0-2)	0.148 *
Hamstring			
Delta Week 2	0.5 (0-1)	0.5 (0-1)	0.202 *
Delta Week 4	1 (0-2)	0.5 (0-2)	0.345 *

Median change in muscle strength before and after intervention was compared from participants in intervention group and control group. A *Mann-Whitney Test was conducted to compare the results, a p-value of <0.05 is considered significant.

Table 6. Comparison of WOMAC Score at Week 4

Delta WOMAC	Intervention Group	Control Group	p-value
Total WOMAC	19 (11-26)	8 (2-16)	<0.001 *
Pain	6 (4-10)	4 (0-6)	<0.001 *
Stiffness	1 (0-3)	0 (0-2)	0.325
Function	11 (5-19)	3 (0-10)	<0.001 *

Median change in WOMAC before and after intervention were compared from participants in intervention group and control group. A *Mann-Whitney Test was conducted to compare the results, a p-value of <0.05 is considered significant.

the benefit of laser therapy in promoting muscle strength in patients with knee OA. A study by Li, et al²⁰ have showed some benefit in improving muscle fatigue by increasing mitochondrial density, angiogenesis and myotube formation. However, further studies is warranted to see the benefits of using laser based therapy to increase muscle strength in patients suffering from knee OA. In this study, the addition of HILT did not display significant improvement in muscle strength when compared to physical therapy alone.

This study is the first in Indonesia to evaluate the effectiveness of HILT in improving functional capacity in patients with knee OA, using the WOMAC index. The results of this study promotes the idea that the addition of HILT therapy to conventional exercise regiments may be beneficial in improving pain and function compared to exercise alone ($p < 0.05$). These findings are in line with previous studies conducted by Kim et al (2016), Alayat et al (2017), Nazari et al (2019), Akaltun et al (2021), dan Siriratna et al (2022).^{12,21-24} One of the possible causes in improved WOMAC score comes from reduced pain sensation experienced by the patient which is in line with the findings observed in this study. Khumaidi, et al²⁵ suggested that patients with knee OA and chronic pain have a tendency to avoid physical activities and exercise despite being aware of its benefits. They often deliberately limit their mobility to prevent pain.

Study Limitation

The limitations of this study include a small sample size, which may not represent the entire knee OA population. The subjects had varying BMI (both non-obese and obese), introducing potential confounding variables as it is independently associated with both the exposure and the outcome (pain, function, strength). Additionally, the therapy duration was limited to 4 weeks, so the long-term effects of HILT remain unexplored.

Conclusion

Based on the findings of this study, the addition of HILT therapy to traditional exercise regiments is beneficial in improving patient with knee OA. This is particularly true in improving pain and function, although the benefits for muscle strength require further investigation. Given the safety and effectivity of HILT, this type of management can be beneficial for high-risk patient patients contraindicated for or unwilling to do surgery.

Acknowledgement

This research was supported by the Faculty of Medicine, Universitas Indonesia as well as Cipto Mangunkusumo Hospital. The author would also like to thank all participants and parties involved in this research.

Ethics and Consent

This study was approved by the Research Ethics Committee of Universitas Indonesia. All methods were carried out in accordance with relevant regulations and guidelines (ethical approval reference number: KET-595/UN2.F1/ETIK/PPM.00.02/2022. Written informed consent was obtained from all participants before the study began.

Competing Interest

The authors declare there are no conflicts of interest.

Grant Information

The author declare that no grants were involved in supporting this work.

Data Availability

Data supporting the findings of this study is available upon request from the corresponding author.

Reference

1. Allen KD, Thoma LM, Golightly YM. Epidemiology of osteoarthritis. *Osteoarthritis Cartilage*. 2022 Feb;30(2):184–95.
2. Lundgren-Nilsson Å, Dencker A, Palsam A, Person G, Horton MC, Escorpizo R, et al. Patient-reported outcome measures in osteoarthritis: a systematic search and review of their use and psychometric properties. *RMD Open*. 2018 Dec;4(2):e000715.
3. Hawker GA. Osteoarthritis is a serious disease. *Clin Exp Rheumatol*. 2019;37 Suppl 120(5):3–6.
4. Tong , Yu H, Huang X, Shen J, Xiao G, Chen L, et al. Current understanding of osteoarthritis pathogenesis and relevant new approaches. *Bone Res*. 2022 Sep 20;10(1):60.
5. Liao CD, Chiu YS, Ku JW, Huang SW, Liou TH. Effects of Elastic Resistance Exercise on Postoperative Outcomes Linked

- to the ICF Core Sets for Osteoarthritis after Total Knee Replacement in Overweight and Obese Older Women with Sarcopenia Risk: A Randomized Controlled Trial. *JCM*. 2020 Jul 11;9(7):2194.
6. Da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, et al. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *The Lancet*. 2017 Jul;390(10090):e21–33.
7. Overton C, Nelson AE, Neogi T. Osteoarthritis Treatment Guidelines from Six Professional Societies: Similarities and Differences. *Rheum Dis Clin North Am*. 2022 Aug;48(3):637–57.
8. Geng R, Li J, Yu C, Zhang C, Chen F, Chen J, et al. Knee osteoarthritis: Current status and research progress in treatment (Review). *Exp Ther Med*. 2023 Aug 25;26(4):481.
9. Mo L, Jiang B, Mei T, Zhou D. Exercise Therapy for Knee Osteoarthritis: A Systematic Review and Network Meta-analysis. *Orthop J Sports Med*. 2023 May;11(5):23259671231172773.
10. Ekici B, Ordahan B. Evaluation of the effect of high-intensity laser therapy (HILT) on function, muscle strength, range of motion, pain level, and femoral cartilage thickness in knee osteoarthritis: randomized controlled study. *Lasers Med Sci*. 2023 Sep 25;38(1):218.
11. Wyszynska J, Bal-Bocheńska M. Efficacy of High-Intensity Laser Therapy in Treating Knee Osteoarthritis: A First Systematic Review. *Photomedicine and Laser Surgery*. 2018 Jul;36(7):343–53.
12. Siriratna P, Ratanasutirantont C, Manisorn T, Santiniyom N, Chira-Adisai W. Short-Term Efficacy of High-Intensity Laser Therapy in Alleviating Pain in Patients with Knee Osteoarthritis: A Single-Blind Randomised Controlled Trial. *Pain Res Manag*. 2022;2022:1319165.
13. Ezzati K, Laakso EL, Salari A, Hasannejad A, Fekrazad R, Aris A. The Beneficial Effects of High-Intensity Laser Therapy and Co-Interventions on Musculoskeletal Pain Management: A Systematic Review. *J Lasers Med Sci*. 2020 Jan 18;11(1):81–90.
14. Zhang R, Zhan L, Sun S, Peng W, Sun Y. Validity of a Newly-Designed Rectilinear Stepping Ergometer Submaximal Exercise Test to Assess Cardiorespiratory Fitness. *J Sports Sci Med*. 2017 Sep;16(3):357–64.
15. Lacio M, Vieira JG, Trybulski R, Campos Y, Santana D, Filho JE, et al. Effects of Resistance Training Performed with Different Loads in Untrained and Trained Male Adult Individuals on Maximal Strength and Muscle Hypertrophy: A Systematic Review. *IJERPH*. 2021 Oct 26;18(21):11237.
16. Angelova A, Ilieva EM. Effectiveness of High Intensity Laser Therapy for Reduction of Pain in Knee Osteoarthritis. *Pain Research and Management*. 2016;2016:1–11.
17. Wu M, Luan L, Pranata A, Witchalls J, Adams R, Bousie J, et al. Is high intensity laser therapy more effective than other physical therapy modalities for treating knee osteoarthritis? A systematic review and network meta-analysis. *Front Med (Lausanne)*. 2022;9:956188.
18. Poenaru D, Sandulescu MI, Potcovaru CG, Cinteza D. High-Intensity Laser Therapy in Pain Management of Knee Osteoarthritis. *Biomedicines*. 2024 Jul 27;12(8):1679.
19. Zeng CY, Zhang ZR, Tang ZM, Hua FZ. Benefits and Mechanisms of Exercise Training for Knee Osteoarthritis. *Front Physiol*. 2021 Dec 16;12:794062.
20. Li C, Chen Y, Lin T, Hsiao Y, Fu JC, Chen C, et al. Immediate responses of multi-focal low level laser therapy on quadriceps in knee osteoarthritis patients. *The Kaohsiung J of Med Scie*. 2019 Nov;35(11):702–7.
21. Kim GJ, Choi J, Lee S, Jeon C, Lee K. The effects of high intensity laser therapy on pain and function in patients with knee osteoarthritis. *J Phys Ther Sci*. 2016 Nov;28(11):3197–9.
22. Alayat MSM, Aly THA, Elsayed AEM, Fadel ASM. Efficacy of pulsed Nd:YAG laser in the treatment of patients with knee osteoarthritis: a randomized controlled trial. *Lasers Med Sci*. 2017 Apr;32(3):503–11.
23. Nazari A, Moezy A, Nejati P, Mazaherinezhad A. Efficacy of high-intensity laser therapy in comparison with conventional physiotherapy and exercise therapy on pain and function of patients with knee osteoarthritis: a randomized controlled trial with 12-week follow up. *Lasers Med Sci*. 2019 Apr;34(3):505–16.
24. Akaltun MS, Altindag O, Turan N, Gursay S, Gur A. Efficacy of high intensity laser therapy in knee osteoarthritis: a double-blind controlled randomized study. *Clin Rheumatol*. 2021 May;40(5):1989–

- 95.
25. Khumaidi MA, Paturusi I, NUSDWIN-
URINGTYAS N, ISLAM AA, GUNAWAN WB,
NURKOLIS F, et al. Is low-level laser ther-
apy effective for patients with knee joint
osteoarthritis? implications and strategies
to promote laser therapy usage. *Front
Bioeng Biotechnol.* 2022;10:1089035.

