


## High-intensity laser therapy (class IV) and ibuprofen gel phonophoresis for treating knee osteoarthritis among people living in hilly terrain: a randomized, double blind, multi-centre trial protocol

### Terapia a laser de alta intensidade (class IV) e fonoforese em gel de ibuprofeno para o tratamento de osteoartrite de joelho entre pessoas que vivem em terreno montanhoso: um protocolo de ensaio multicêntrico, duplo-cego randomizado

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**ABSTRACT | INTRODUCTION:** People living in hilly terrain with abnormal cyclic loading could lead to bone cartilage degeneration. High-intensity laser therapy (HILT) and Ibuprofen gel phonophoresis (IGP) have innumerable benefits for patients with knee osteoarthritis (KOA). However, it is still unclear which treatment is effective among them in rehabilitating patients with KOA. **OBJECTIVE:** To verify whether 8-week HILT is no worse than the IGP in treating patients with knee osteoarthritis living in hilly terrain. **MATERIALS AND METHODS:** A total of 108 individuals with KOA will be recruited by simple random sampling to participate in a randomized, double-blind, controlled study. Recruited individuals with KOA will be randomly divided into two groups, the HILT group (experimental group) and the IGP group (active control group). The treatment duration of HILT and IGP will be 8 minutes in one session/knee joint for each day for 3 days/week up to 8 weeks in addition to their conventional exercises for 30 minutes. The Western Ontario and McMaster Universities Osteoarthritis Index, Digitalized pain pressure algometer, and 36-Item Short-Form Health Survey questionnaire are the outcome measures that will be recorded at baseline, end of the 8-week post-intervention period. **PERSPECTIVES:** The results from this trial will contribute to evidence-based recommendations for the clinical implication of whether HILT is no worse than IGP, along with exercise intervention for treating individuals with KOA living in hilly terrain.

**KEYWORDS:** Knee osteoarthritis. Uphill. Incline walking. Degeneration. Laser therapy. Ultrasound.

**RESUMO | INTRODUÇÃO:** Pessoas que vivem em terrenos íngremes com carga cíclica anormal podem levar à degeneração da cartilagem óssea. A terapia a laser de alta intensidade (TLAI) e a fonoforese trazem inúmeros benefícios aos pacientes com osteoartrite de joelho (OAJ). No entanto, ainda não está claro qual tratamento é eficaz entre eles na reabilitação de pacientes com OAJ. **OBJETIVO:** Verificar se a TLAI de 8 semanas não é pior que a fonoforese em gel de ibuprofeno (FGI) no tratamento de pacientes com osteoartrite de joelho que vivem em terreno montanhoso. **MATERIAIS E MÉTODOS:** Um total de 108 indivíduos com OAJ serão recrutados por amostragem aleatória simples para participar de um estudo randomizado, duplo-cego e controlado. Os indivíduos recrutados com OAJ serão divididos aleatoriamente em dois grupos, grupo TLAI (grupo experimental) e grupo FGI (grupo controle). A duração do tratamento de TLAI e FGI será de 8 minutos em uma sessão/articulação do joelho para cada dia, por 3 dias/semana até 8 semanas, além de seus exercícios convencionais por 30 minutos. O Western Ontario and Mc Master Universities Osteoarthritis Index, o algômetro digitalizado de pressão de dor e o questionário de 36 itens Short-Form Health Survey são as medidas de resultado que serão registradas ao término, no final do período pós-intervenção de 8 semanas. **PERSPECTIVAS:** Os resultados deste ensaio contribuirão para recomendações baseadas em evidências para a implicação clínica de que o TLAI não é pior que o FGI juntamente com a intervenção de exercício para tratar indivíduos com OAJ que vivem em terreno íngreme.

**PALAVRAS-CHAVE:** Osteoartrite do joelho. Morro acima. Caminhada inclinada. Degeneração. Terapia à laser. Ultrassom.

## Introduction

One of the world's leading causes of disability and pain is osteoarthritis (OA).<sup>1</sup> OA is a chronic, slowly progressive, degenerative joint disease that affects articular cartilage and is accompanied by pain, swelling, and dysfunction.<sup>2</sup> OA is often considered a severe joint disease as it has a negative impact on the quality of life.<sup>3</sup> Among the elderly population, it is the primary cause of reduced mobility. About 20% of Indians have reported having knee OA from 30 years of age and above.<sup>4,5</sup> Approximately 40% of women above 65 years of age reported the symptoms of knee OA while 70% of women were found to be radiologically positive for knee osteoarthritis (KOA).<sup>6</sup> People who live in hilly areas have aberrant cyclic loading, which can contribute to cartilage deterioration over time.

Non-pharmacological treatments such as ultrasound therapy, transcutaneous electrical nerve stimulation, interferential therapy, shortwave diathermy, and others slow the progression of knee osteoarthritis. Laser therapy and ultrasound combined with Nonsteroidal anti-inflammatory drug (NSAID) (Phonophoresis/pharmacological agent) are proven to be effective to minimized drug interaction in systemic circulation. People who live in uphill terrain experience cyclic overloading in their knee joints, which leads to cartilage deterioration over time. KOA patients can choose from a variety of therapeutic options. Exercise is a primary non-pharmacological treatment for OA, according to international standards for its management. Exercise is relatively safe and helps people feel better overall and with their ailments.<sup>7</sup> For conservative treatment, phonophoresis and laser therapy are two options. Laser therapy has proven to be one of the most promising treatments for KOA patients.<sup>7,8</sup> Eighteen randomised controlled/clinical trials (RCTs) investigating the effects of low-level laser therapy in KOA treatment are available.<sup>8-24</sup> Only two RCTs illustrate the usefulness of high-intensity laser therapy (HILT)<sup>17,23</sup>, while sixteen RCTs emphasise the benefits of low-level laser therapy (LLLT).<sup>8-14,16-23</sup> The majority of them emphasise the efficacy of low-level laser therapy in the treatment of KOA. Seven RCTs on phonophoresis treatment have been completed and

shown to be successful. However, no research has been done to compare the effectiveness of HILT and phonophoresis in KOA patients' treatment. Therefore, there is a definite need to evaluate the efficacy of HILT and phonophoresis among individuals with KOA who live in hilly areas.

The objective of this study is to verify whether 8-week HILT is no worse than the ibuprofen gel phonophoresis (IGP) in treating patients with knee osteoarthritis living in hilly terrain.

## Hypothesis

There will be no significant difference in pain and quality of life after HILT intervention when compared to IGP in the experimental and active control groups is the null hypothesis. While in the alternative hypothesis, there will be significant changes in pain and quality of life after the application of HILT when compared to IGP.

## Methods

### Study design

This protocol study design will be a two-group pre-test/post-test, double-blinded, randomized clinical study. The outcome assessor and therapist will be blinded in the study. The study protocol was approved by the institutional research and ethics committee (MMDU/IEC/140E on 25/03/2020). The study will be done strictly in accordance with the guidelines of the Helsinki declaration, revised in 2013.<sup>25</sup> The study will also follow the ethical guidelines issued by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) titled "International Ethical Guidelines for Health-related Research Involving Humans",<sup>26</sup> 2016. After obtaining ethical approval from the institutional ethics committee, a unique Universal Trial Number (UTN) U1111-1237-6893 was obtained for the study. The study protocol was uploaded to open access

clinical trial registry platform, Clinical Trials Registry (NCT04320914) (<https://clinicaltrials.gov/ct2/show/CT04320914?term=NCT04320914&draw=2&rank=1>) registered on 25 March 2020 (updated on 16 June 2020), approved by WHO's International Clinical Trials Registry Platform (ICTRP) and International Committee of Medical Journal Editors (ICMJE). The data will be collected from tertiary referral hospital settings and old age homes. Written informed consent will be taken from the participants before their enrolment in the study.

## Participants

This study aims to recruit, according to American College of Rheumatology (ACR's) diagnostic criteria, patients diagnosed with clinical KOA.<sup>27</sup> The ACR clinical classification criteria is a popular method of classifying KOA. In this criterion, the presence of knee pain along with at least three of the following six items can classify the KOA in the patients:

1. Age > 50 years old
2. Morning stiffness < 30 minutes
3. Crepitus on knee motion
4. Bony tenderness

5. Bony enlargement

6. No palpable warmth

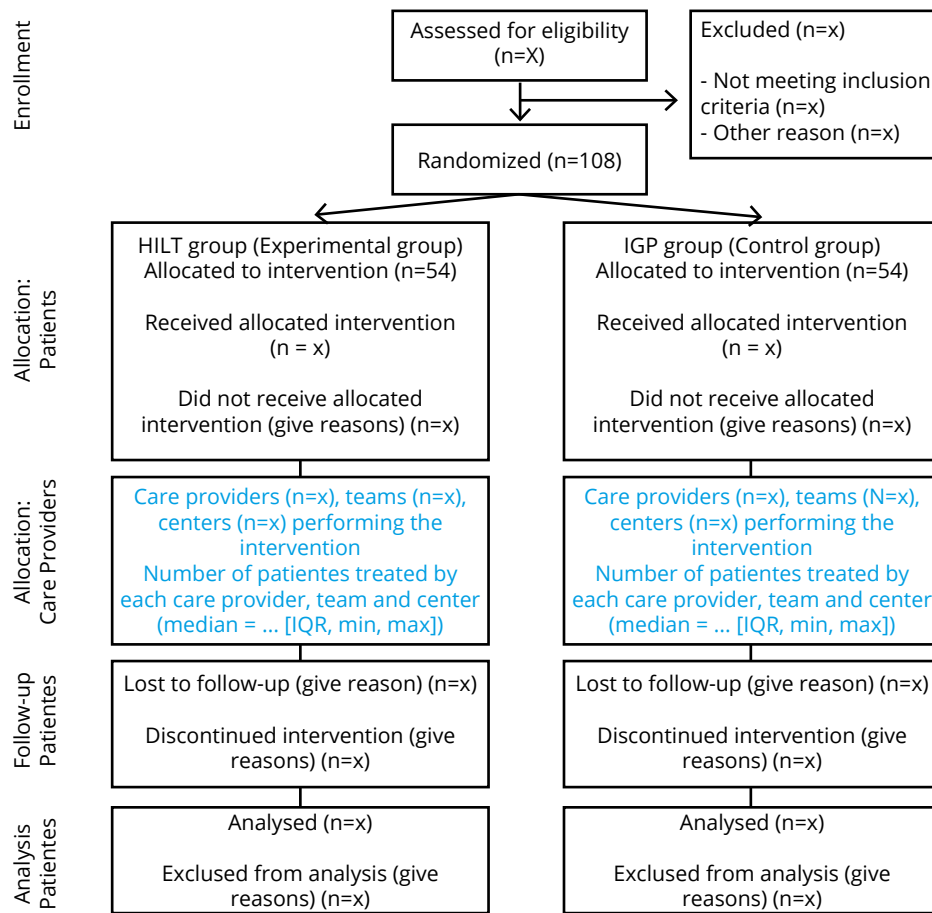
Participants will be recruited from recognized tertiary care hospitals.

## Randomization and allocation concealment

After the demographics, recruited 108 individuals with KOA will be randomly divided into two groups, the HILT group (Experimental group) and the IGP group (Control group), with block randomization. There will be four blocks, with the matrix design of 4 x 27, where 27 being rows. Each row has four blocks containing four chits (2 chits for each group). The individuals with KOA will be allotted to the group based on the chit randomly chosen by them. Once the block is allocated, the next row block was opened. Thus, an equal number of individuals with KOA will be assigned to each group over time. Individuals with KOA in the HILT group will be provided with HILT. The IGP group will receive phonophoresis with ibuprofen gel, and pre-post changes in the outcome measures will be documented.

The study design's blueprint is explained with a flow diagram for individual randomized controlled trials of non-pharmacologic treatments<sup>28</sup> to be adopted, displayed in Figure 1.

**Figure 1.** Flowchart of the study



Source: The authors (2022).

### Eligibility criteria

### Inclusion criteria

1. People living in hilly terrain for the last six months,
2. Patients diagnosed with clinical chronic KOA according to the diagnostic criteria of ACR were included in the study,
3. Patients between grade II-IV, according to Kellgren Lawrence grading system of radiological classification of KOA,
4. Age between 45-70 years,
5. Both male and female.

### Exclusion criteria

1. Recent history (within the last six months) of the intra-articular procedure (injection and/or lavage) to the knee;
2. Any known history of knee surgery/fracture,
3. Acute synovitis/arthritis, including infectious conditions,
4. Patients undergoing radiation therapy,

5. Other secondary co-morbidities (known cardiac diseases).

### Sample size calculation

The number of participants was calculated by the formula<sup>29</sup>  $2 [(Z\alpha + Z\beta) S / d]^2$  estimated using the 90% power by substituting 12.5 minimal clinically important difference (MCID)<sup>30</sup> and 48.5<sup>12</sup> as pooled standard deviation (SD). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is considered a primary outcome in the current study, so results reported by Salehi et al.<sup>30</sup> were used in the sample size estimation. By the sample size estimation, we have obtained a minimum of 54 in each group, including 10% dropouts to participate in this two-group randomized controlled trial study. 108 individuals with KOA will be recruited by convenience sampling.

### Outcome assessment

Outcomes will be assessed at baseline, at 4-week and at the end of the 8-week post-intervention period.

1. Digitalized pain pressure algometer (ALGO-DS-01)
2. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
3. 36-Item Short-Form Health Survey (SF-36)

### Primary outcome measure

1. A digitalized pain pressure algometer

Pain intensity will be measured using a calibrated digitalized pain pressure algometer (ALGO-DS-01) in individuals with KOA. The sensor digital algometer is a force gauge with the computer, which is highly accurate. The ALGO-DS-01 is chosen to assess pain for Mechanical sacroiliac joint dysfunction (SIJD), a reliable and valid tool for evaluating sacroiliac joint dysfunction. The inter-rater reliability of the pressure pain algometer was demonstrated to be moderate to good, with an intraclass correlation coefficient (ICC) of (0.62-0.84).<sup>31</sup> The pain pressure threshold will be determined using a handheld electronic pressure algometer with a 1 cm<sup>2</sup> probe area with

an increase of the pressure rate of 20 Kpa/s. The pressure algometer consists of a "pistol" handle and a rod with a pressure-sensitive gauge strain at the tip. All the measurements will be performed at 1 cm distal from the medial knee joint line with the knee flexed at 90°.

2. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC will be used to evaluate the disease-specific self-reported symptoms of OA.<sup>32</sup> This form is comprised of 24 questions in three categories, including pain (5 questions), stiffness (2 questions), and physical function (17 questions). These 24 items are presented on a five-point Likert (0-4) scale, where higher scores indicate the higher intensity of the related symptom. Scores were summed to yield a sum score of 0-20, 0-8, and 0-68 for pain, stiffness, and physical function subscales, respectively. The test-retest reliability of WOMAC was demonstrated to be good reliability, with ICC values of the three dimensions: pain, stiffness, and physical function being 0.80, 0.77, and 0.89, respectively.

The minimal clinically significant difference of WOMAC at two months of intervention is 12.5.<sup>30</sup>

### Secondary outcome measure

3. 36-Item Short-Form Health Survey (SF-36)

The 36-Item Short-Form Health Survey questionnaire (SF-36) is a very popular instrument for evaluating Health-Related Quality of Life (QoL). The SF-36 measures eight scales: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). There are two distinct concepts measured by the SF-36: a physical dimension, represented by the Physical Component Summary (PCS), and a mental dimension, represented by the Mental Component Summary (MCS). SF-36 is used to assess QoL in a patient with KOA.<sup>33,34</sup> The reliability of SF-36 was demonstrated to be good, with ICC values greater than 0.75 except for the social functioning.

A brief Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) schedule is provided in Figure 2.

Figure 2. Study Protocol

	Study Period										
	Enrolment	Allocation	Post-allocation (Treatment)								Follow-up (Evaluation)
TIMEPOINT**	0 week	1 week	1 week	2 week	3 week	4 week	5 week	6 week	7 week	8 week	8 week
ENROLMENT:											
Eligibility screen	X										
informed consent	X										
Randomization	X										
Allocation		X									
INTERVENTIONS:											
HILT group interventions			X	X	X	X	X	X	X	X	
IGP group interventions			X	X	X	X	X	X	X	X	
ASSESSMENTS:											
Demographic data	X										
Algometer	X					X					X
WOMAC	X					X					X
SF-36	X					X					X

Source: The authors (2022).

## Intervention

### High intensity-laser therapy (HILT) group/Experimental group

Forty individuals with KOA in the HILT group will receive Class IV LASER therapy. A Class IV LASER emits power of more than 500 mW.<sup>35</sup> The patient and therapist will wear the safety eyewear for eye protection from LASER rays before its administration (iLux LF HPS D15, Mectronic). The program on the LASER machine will be selected, and the dosage will be delivered accordingly. The handpiece will be positioned in contact and perpendicularly.

In contrast, the patient is in a supine lying position with the knee flexed at 30° to open the joint surfaces to the laser beam (optical windows). The scanning will be performed transversely and longitudinally in the anterior, medial, and lateral aspects of the knee joint, emphasizing the application in the joint line between the tibial and femoral epicondyles.<sup>23</sup> The total energy delivered to the patient during one session was 1,250 J through three phases of treatment. The initial phase will be performed with fast manual scanning, with a total of 500 J. In the initial phase, the laser fluency will be set to two successive subphases of 710 and 810 mJ/cm<sup>2</sup> for a total of 500 J. In the intermediate phase, the handpiece will be applied on the joint line just proximal to the medial and lateral tibial condyles with 25 J, a fluency of 610 mJ/cm<sup>2</sup>, and 14s for each point and a total of 250 J in this phase. The final phase will be the same as the initial phase (500 J) except that scanning will be slow manual scanning. The application time for all three phases will be approximately 15 min, with the total energy delivered to the patient during one session of 1,250 J.<sup>17</sup> The device will calculate the energy received in each phase and the total energy produced to the patient during the treatment session. The duration of the treatment will be 8 minutes in one session/knee joint for each day for three days/week for eight weeks. Thus, each patient with KOA will receive 24 sessions in total. The daily reminder WhatsApp messages will be sent during the eight weeks intervention period to minimize the dropouts.



## Ibuprofen gel phonophoresis (IGP) group/Active Control group

Individuals with KOA in the IGP group will be administered with continuous ultrasound set at a frequency of 1 MHz. An intensity of 1 W/cm<sup>2</sup> was applied on a circular basis.<sup>36</sup> Each treatment session will last for 8 min, with one session each day for three days/week for eight weeks. Thus, each patient with KOA will receive 24 sessions in total. 40 individuals with KOA will be asked to undergo baseline measurements and eight weeks of post-intervention measurements. During the study period, if they get ill, the history of medications will be noted.

### Exercise intervention

Exercise intervention will be provided to both groups. An individual with KOA will be educated on doing the set of exercises correctly at their home during the first session. Standardized exercise protocol for KOA, which consists of nine activities including muscle strengthening and flexibility training<sup>37,38</sup> as follows: 1. Warm-up exercises: Walking at the usual speed on a flat surface for 10 min with hamstring and gentle calf stretches. 2. Hamstring and calf gentle stretches. 3. Unilateral straight leg raise (SLR). 4. Quadriceps isometric. 5. Pillow squeeze (pillow placed between the legs with knee bent 90). 6. Bilateral heel raise. 7. Single limb stance. 8. Step-ups (step height 7–8 inches). 9. Quadriceps strengthening exercises (starting weight of 10 repetition maximum).

A detailed description of the intervention is mentioned in Table 1.

**Table 1.** Detailed description of the intervention

Intervention	Dosage Prescription
<b>1. High-intensity LASER therapy (HILT)</b> [Therapeutic high-intensity laser typically has a semiconductor diode and produces light of one specific wavelength, and is capable of deep penetration into tissue]	The total energy that will be delivered to the patient during one session will be 1,250 J through three phases of treatment. <ol style="list-style-type: none"> <li>Initial phase (710 and 810 mJ/cm<sup>2</sup> for a total of 500 J)</li> <li>Intermediate phase (hand-piece will be applied on the joint line just proximal to the medial and lateral tibial condyles with 25 J, a fluency of 610 mJ/cm<sup>2</sup>, and a time of 14s for each point and a total of 250 J)</li> <li>Final phase (same as the initial phase (500 J) except that scanning will be slow manual scanning )</li> </ol> The application time for all three phases will be approximately 15 min with the total energy delivered to the patient during one session of 1,250 J
<b>2. Ibuprofen gel phonophoresis</b>	Continuous ultrasound set at a frequency of 1 MHz and an intensity of 1.0 W/cm <sup>2</sup> will be applied on a circular basis (8 min/session/day X 3 days/week X 8 weeks)
<b>3. Conventional physiotherapy</b> (Nine exercises, including muscle strengthening and flexibility training)	<ol style="list-style-type: none"> <li>Warm-up exercises: Walking at the usual speed on a flat surface for 10 min, 10 reps X 3 sets with 3 min rest in between the sets</li> <li>Hamstring and calf gentle stretches: 5 reps X 3 sets with 30-second hold time and 3 min rest in between the sets</li> <li>Unilateral Straight leg raise (SLR): 10 reps X 3 sets with 3 min rest in between the sets</li> <li>Quadriceps isometric: 10 reps X 3 sets with 3 min rest in between the sets, each contraction held for 4 seconds</li> <li>Pillow squeeze (pillow placed in between the legs with knee bent 90): hold for 5 seconds X 10 reps X 3 sets with 3 min rest in between the sets</li> <li>Bilateral heel raise (in a standing position with the support of a wall): 10 reps X 3 sets with 3 min rest in between the sets</li> <li>Single limb stance: stand for 30 seconds X 5 reps X 3 sets with 3 min rest in between the sets</li> <li>Step ups (step height 7-8 inches): 10 reps X 3 sets with 3 min rest in between the sets</li> <li>Quadriceps strengthening exercises (starting weight of 10 repetition maximum): 10 reps X 3 sets with 3 min rest in between the sets</li> </ol>

Source: The authors (2022).

## Statistical analysis

The collected demographic and outcome measures will be assessed for their normality using the Kolmogorov-Smirnov test. Per-protocol analyses are preferable over intention-to-treat (ITT) analyses because they reduce the probability of type I errors in non-inferiority trials<sup>39</sup>. As a result, only patients who have finished their treatment will be included in the main analysis, which will be a per-protocol analysis. To enhance confidence in the results of sensitivity analyses, ITT analyses will be employed, regardless of whether participants finished the treatment or not. In order to investigate the differences between groups, the time of assessment will be considered a fixed variable.<sup>40</sup> When the two-sided 95% confidence interval (the range of plausible differences between the two treatments) lies entirely above the MCID of 12.5<sup>30</sup>, which is the non-inferiority margin and the smallest clinically acceptable difference, HILT is considered non-inferior as compared with IGP for the primary outcome, pain and disease-specific self-reported symptoms of OA. Though, the priori sample size calculation is performed, Post hoc (retrospective) power analysis will be performed using G\* Power 3.1.9.4 software<sup>41</sup> to re-calculate the power of the study with the sample size of 40 in one group and reported effect size at the end of the study. All the data will be analyzed using statistical software, statistical package for social science (SPSS), IBM SPSS version 20.0 (Armonk, NY: IBM Corp.). The p-value  $\leq 0.05$  was considered to be statistically significant.

## Withdrawal

A participant will be withdrawn from the study after inclusion if one of the following conditions occurs:

- Patients' withdrawal of the informed consent, whatever the reason;
- Patients refusal to attend the two consecutive visits
- Any infections/injuries
- Death

## Discussion

This article presents a detailed description of a randomized controlled trial designed to analyze the results in pain and quality of life by HILT and phonophoresis intervention for individuals with KOA. By observing the effects of HILT and phonophoresis, we will analyze and understand the mechanism that causes pain and quality of life affected by KOA patients.

By absorbing and permeating therapeutic medications through the skin, phonophoresis uses ultrasound to deliver the drugs. Many musculoskeletal problems have been shown to benefit from phonophoresis using an anti-inflammatory gel to reduce pain and inflammation. Despite the widespread use of phonophoresis, there is not enough scientific evidence to support treatment, particularly concerning osteoarthritis of the knee that has been symptomatic.

A previous study examined the effectiveness of high-intensity LASER therapy to reduce pain in knee osteoarthritis.<sup>42</sup> They have reported that pain level was reduced after seven days of treatment and long lasting for three months. This study had some limitations, such as a pilot study with a small sample size and less study duration. In the study, we will be using HILT to treat pain and improve patients' quality of life with chronic knee osteoarthritis. HILT provides both thermal and mechanical effects and produces an electromagnetic field and photoelectric effect on the tissues. HILT has deeper penetration (3-4 cm)<sup>43</sup> ability wavelength with a range from 700 to 1000 nm, which represents the near-infrared radiation and is commonly used in clinical treatment. HILT produces slow light absorption via chromophores, improves mitochondrial oxidative reactions, and increases ATP, DNA, and RNA production.<sup>44</sup> Pain reduction due to high-level LASER therapy occurs because of increasing the ability to produce morphine-mimetic substances and inhibit pain impulses. By modifying the components of the inflammatory response, exudation, proliferation, and preventing cyclooxygenases, lipooxygenases influence prostaglandins, and prostacyclin formation, HILT has an anti-inflammatory effect. In their review article, Wszyńska and Bal-Bocheńska concluded that



there is evidence that HILT provides an analgesic effect in acute and chronic KOA.<sup>45</sup> Therefore, our study will be using HILT with optimal dosage and establish the effectiveness of HILT.

To date, there are limited studies on the effectiveness of using HILT and phonophoresis intervention in therapeutic effect use. Therefore, this study will aim to determine the HILT or IGP effectiveness on patients' pain threshold and quality of life suffering from KOA.

## Perspectives

The results from this trial will contribute to evidence-based recommendations for the clinical implication of whether HILT is no worse than IGP, along with exercise intervention for treating individuals with KOA living in hilly terrain.

## Authors' contributions

Srivastav AK, Saini V, and Samuel AJ participated in the conception and design of the study. Srivastav AK, Sharma D, Saini V, and Samuel AJ participated in data acquisition, data analysis and/or interpretation, manuscript writing, and critical manuscript review for important intellectual content. All authors approved the version of the manuscript to be published.

## Conflicts of interest

No financial, legal or political conflicts involving third parties (government, companies and private foundations, etc.) were declared for any aspect of the submitted work (including, but not limited to grants and funding, participation in an advisory board, study design, preparation manuscript, statistical analysis, etc.).

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