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Pain Efficacy of a Home-Based Low-Intensity Continuous Ultrasound Stimulator for Knee Arthritis: A Single-Arm, Open-Label, Prospective Clinical Trial

Md. Habibur Rahman[1*], Yeon-Gyu Jang[2*], Johny Bajgai[1], Subham Sharma[1], Kchorng Vira[1], Abdul-Nasir Sofian[1,3], Seong Hoon Goh[1], Yundeok Kim[4], Cheol-Su Kim[1], Doo-Sup Kim[5#], Kyu-Jae Lee[1,3#]

[1]Department of Convergence Medicine, Wonju College of Medicine, Yonsei University, Wonju, Republic of Korea
[2]Department of Neurosurgery, Wonju Severance Christian Hospital, Wonju College of Medicine, Yonsei University, Wonju, Republic of Korea
[3]Department of Global Medical Science, Wonju College of Medicine, Yonsei University, Wonju, Republic of Korea
[4]Department of Internal Medicine, Division of Hematology-Oncology, Wonju Severance Christian Hospital, Wonju, Republic of Korea
[5]Department of Orthopaedic Surgery, Wonju College of Medicine, Yonsei University, Wonju, Republic of Korea
Email: globaldreamer1990@yonsei.ac.kr, johnybajgai@yonsei.ac.kr, subhamsharma047@gmail.com, kchorng.15vira@gmail.com, forget419@yonsei.ac.kr, cs-kim@yonsei.ac.kr, #medbio@yonsei.ac.kr, nsjyg@naver.com, abdulnasirsofian62@gmail.com, autunnale0910@yonsei.ac.kr, #dskim1974@yonsei.ac.kr

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Abstract

1) Background: Osteoarthritis (OA) is defined as a degenerative joint disease that mainly affects the bone. This study aims to evaluate the effect of low-intensity continuous ultrasound (LICUS) treatment on the knee of osteoarthritis patients through home-based intervention using the LICUS medical device. 2) Methods: The clinical trials were designed in a single-arm, open-label, and intervention study. Thirty-five participants, including those who dropped out (12%), were screened and enrolled. The patients received LICUS (1.1 MHz, 1.5 W/cm^2, collimated beams) on the knee by the instructions of the investigator at home (5 min/session, 3 times/day, for four-weeks). Outcome measures were assessed using the Visual Analog Scale (VAS) as a primary endpoint and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) as a secondary endpoint to evaluate pain relief and functional recovery of the knee between pre-treatment (baseline) and post-treatment (four-weeks). 3) Results: Knee pain scores measured using the VAS and WOMAC indices were significantly reduced after a four-week treatment with LICUS compared to baseline. Knee stiffness and functional

*Md. Habibur Rahman and Yeon-Gyu Jang have equally contributed to this paper as a first author.

capacity were significantly reduced after the LICUS application. In addition, there were no reports of adverse effects during the study period. 4) Conclusion: Long-term and home-based application of LICUS can be recommended as an alternative option for the treatment of OA patients, as evidenced by the effect of pain relief and knee function recovery.

Keywords

Knee Osteoarthritis, Low-Intensity Continuous Ultrasound Stimulator, Clinical Trial, Visual Analogue Scale, Western Ontario and McMaster Universities Osteoarthritis Index

1. Introduction

OA is a degenerative joint disease that mainly affects the bone and cartilage. OA is most common in individuals over 55 years of age [1]. It is a common disease with a prevalence of more than 80% and is considered a normal result of aging, also called arthritis, which is caused by gradual damage or degenerative changes in the cartilage that protects the joint [2]. It is accompanied by inflammation and pain due to damage to the bones and ligaments that make up the joints in OA [3]. Structural changes such as cavity stenosis, cartilage hardening, and cystic formation have been observed [4]. OA is divided into primary (or idiopathic) arthritis and secondary arthritis depending on the cause. Primary OA refers to a case without a specific organic cause and refers to the lumbar spine, hip joint, and knee canal. Secondary arthritis can damage the articular cartilage. Several mechanical stimuli or inflammation, such as the destruction of the matrix macromolecule by enzymatic reactions, metabolic changes brought on by vaginal damage or change, and chondrocytes responding to tissue damage, have been linked to the pathological pathogenesis of OA, although this is not fully understood [5]. Patients with OA usually do not have systemic symptoms and initially show local joint pain [6]. Therefore, fractures increase intramedullary pressure, and joint instability that can cause elongation of the fracture membrane or muscle spasm, and a decrease in atmospheric pressure may increase the relative pressure in the joint cavity. In addition, joint movement disorders may become severe in the vitreous joint (loose bodies). These clinical symptoms usually progress slowly, and sometimes the process is repeated, intermittently improving, and then worsening. OA is the most common disease caused by musculoskeletal pain and disability in the elderly worldwide [7]. The Visual Analog Scale (VAS) and the pain subscale of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) are commonly employed self-administered measures for evaluating the severity of joint pain in individuals with knee or hip OA.

Although there are various treatment strategies for OA, there are no medicinal products that can alter the onset or occurrence of injury-induced structural damage. Therefore, the main goal of arthritis treatment is to relieve pain and maintain

the mechanical range of motion of the joint through conservative treatment. The focus is generally on eliminating the elements of damage to the basement and joints. In addition, weight control, exercise therapy, cold and heat therapy, electrical stimulation therapy, and ultrasound therapy have been applied. Ultrasound is an acoustic pressure wave with a frequency above the human hearing range (16 Hz - 20 kHz pressure wave) and is a form of mechanical energy transmitted through living tissue. It is also widely used as a surgical tool in the medical field. Although the knee joint can be affected, weight-bearing joints such as the knee are particularly susceptible to OA. Medical ultrasound stimulators depend on ultrasound parameters, such as frequency, wavelength, energy, power, and intensity [8] [9]. An ultrasonic intensity of 10 W/cm^2 or higher generates heat. On the other hand, low-intensity ultrasound (20 - 1000 mW/cm^2) produces very little heat, depending on the frequency, wavelength, and treatment duration [10]. There are two US models, whereas, pulsed ultrasound (PUS) predominantly induces non-thermal effects to boost tissue metabolism, improve the extensibility of fibrous tissue, and raise the pain threshold and has very little thermal effects, in contrast, continuous ultrasound (CUS) induces more thermal effects by facilitating tissue regeneration processes that is more beneficial for increasing tissue temperature and altering cell membrane permeability [11] [12]. In addition, CUS can help relieve musculoskeletal pain by increasing local temperature, vasodilation, and metabolism. Furthermore, CUS has been reported to be effective as a stand-alone or adjunctive treatment for soft tissue pain in several studies, and Muftic *et al.* found that its improved VAS for pain [13]. CUS delivered at lower intensity exhibits thermal effects in comparison to PUS. Moreover, evidence suggests that CUS may yield a heightened efficacy in alleviating pain [14]. According to the results of a study comparing the effectiveness of therapeutic ultrasound and simulated ultrasound, it was reported that therapeutic ultrasound can be effective in reducing pain and improving physical function in patients with knee OA [15]. The prevalent parameters for the application of low-intensity ultrasound include an intensity of 0.03 W/cm^2 (alternatively referred to as 30 mW/cm^2) and a frequency of 1.5 MHz [16]. Secondary functional measures, such as mobility, stiffness, and pain, showed significant improvements. Draper *et al.* suggested that LICUS may be an effective noninvasive treatment for knee OA [17]. Therapeutic ultrasound at a frequency of 1.5 MHz has been documented as beneficial in alleviating pain and enhancing physical functionality in individuals with knee osteoarthritis.

At the tissue and cellular levels, shocks from minimal thermal effects are used for pain relief, while longer-type ultrasound exerts both mechanical and thermal effects on tissues and cells. Therefore, the primary aim of this study was to investigate the pain effects of four-weeks of measurements including the degree of knee pain, knee stiffness, and knee function in daily life, as evaluated by the VAS and WOMAC index. Thus, OA, which affects more than 80% of people over 55, plays a major role in the global incidence of musculoskeletal pain and disability. No medication can reverse the start of OA or the structural damage it causes,

despite the wide range of therapy options available. This emphasizes the need for efficient non-invasive treatments. With the VAS and the WOMAC serving as assessment instruments, this study aims to determine whether LICUS effectively reduces knee pain and stiffness and enhances knee function in daily life over a four-week period.

2. Materials and Methods

2.1. Study Design

This study was approved by the Institutional Review Board of Wonju Severance Christian Hospital, Yonsei University, Wonju, Republic of Korea, and was conducted in compliance with the Declaration of Helsinki [18], the Good Clinical Practice guidelines [19], and local regulatory requirements (IRB Number: CR222008). This study was designed as a single-arm, open-label, and intervention study to explore the efficacy of LICUS treatment on the knees of OA patients. All participants were informed of the purpose, protocol, and risks of this clinical study. Intervention was home-based self-treatment for four-weeks from October 10 to November 23, 2022. All participants gave their consent in writing before taking part in the study. This clinical trial was registered in clinical Trals.gov (Identification number NCT05657535) on December 25, 2022. According to Levent *et al.*; 1 W/cm^2 personal ultrasound stimulator during the test, treatment-induced VAS decreased by 42.8% in the experimental group and 20.6% in the control group [20]. Pain treatment response was assessed based on whether the response rate was greater than 80% for four-weeks. Estimation of the number of subjects is a constant for two consecutive independent averages. Sample size calculation was performed using the following normative test formula.

$$N = \frac{2(Z\alpha + Z\beta)\delta 2}{(Uc - Ut)2}$$

N = population size

α = significance level (0.05)

β = power (0.8)

δ = the anticipated differences

Uc-Ut: 1.96 the difference mean

$Z\alpha$: 0.84 at the significance level of 5%

$Z\beta$: at power of 80%

2.2. Participants

Patients with OA were recruited between July and October 2022 and signed an informed consent form before all procedures. Thirty-five participants, including those who dropped out (20%), were screened and enrolled.

2.2.1. Inclusion Criteria

- Individuals aged 40 to 60 years experiencing knee pain caused by OA can walk voluntarily.

- Presence of multiple osteophytes in the tibiofemoral joint observed on X-ray.
- VAS scores ranging from 0 to 10, with 0 indicating no pain and 10 indicating the most severe pain.
- Ability to adhere to physician's guidance, including joint motions.
- Compliance with permitted and prohibited drugs, as well as relief medications.
- Capacity to maintain consistent exercise and activity throughout the clinical trial.
- Full understanding of the trial's objectives and procedures.

2.2.2. Exclusion Criteria

- History of rheumatoid arthritis or gouty arthritis, or peripheral pain aside from the knee joint.
- Evidence of fractures or dislocations on basic radiological assessment.
- Likelihood of neuromuscular conditions.
- Participation in other clinical trials within 6 months before the current trial.
- Intense knee joint pain, excluding conditions like angular deformity or instability within the index knee.
- Presence of tumors other than degenerative knee arthrosis.
- Systemic symptoms that may affect knee pain.
- Pregnancy or lactation.

34 participants were instructed on how to apply the LICUS home medical device are shown in **Figure 1** (JT5, Maeil Tech Co., Seoul, Republic of Korea) to the knee for self-treatment. Each patient self-treated LICUS using a 47-mm diameter applicator after application of acoustic gel on the painful area of the knee for 5 min/session, 3 sessions per day for four-weeks. 1.1 MHz frequency in continuous wave mode and 1.5 W/cm^2 intensity were applied to the patients. Effective radiation area of the device was 6.80 cm^2 ± 20%.

Figure 1. LICUS home medical device JT5 knee pain measurement procedure.

2.3. Outcome Measures

The primary outcome was the change in pain intensity using the VAS scale measured at baseline and after four-weeks of treatment. In this study, a numeri-

cal rating scale ranging from 0 (no pain) to 10 (maximum pain) was used to assess pain severity.

As a secondary outcome, the WOMAC index (3.1 Likert version) was used to assess pain, stiffness, and physical function of the knee in patients with OA. The WOMAC index has been validated as a disease-specific self-report questionnaire to measure the health state of OA in the knees. The questionnaire (total 24 questions) was divided into three categories [knee pain in daily activities (5 questions), knee stiffness after awakening and at daytime (2 questions), and knee functional capacity in daily activities (17 questions)], and each question has a 5-point Likert scale ranging from 0 to 4:0: none, 1: mild, 2: moderate, 3: severe, or 4: extreme. The total score ranged from 0 (best) to 98 (worst). The final WOMAC score was determined by adding the aggregate scores of the three categories to the maximum score. A lower score indicates an improvement in symptoms.

2.4. Statistical Analysis

All statistical analyses were conducted utilizing Prism (version 8.0, GraphPad Software, USA). The data was expressed as the mean ± standard deviation (SD). The VAS scores were subjected to statistical analysis through a one-sample t-test, comparing baseline values with those at four weeks post-treatment. Additionally, WOMAC scores were assessed using an unpaired t-test, comparing baseline scores to those at four weeks post-treatment. Statistical significance was defined as $p < 0.05$.

2.5. Enrollment and Baseline Demographics of the Patient Population

A total of 35 patients were screened, of which 34 were enrolled in a single arm (Figure 2). During the intervention period, three patients dropped out due to

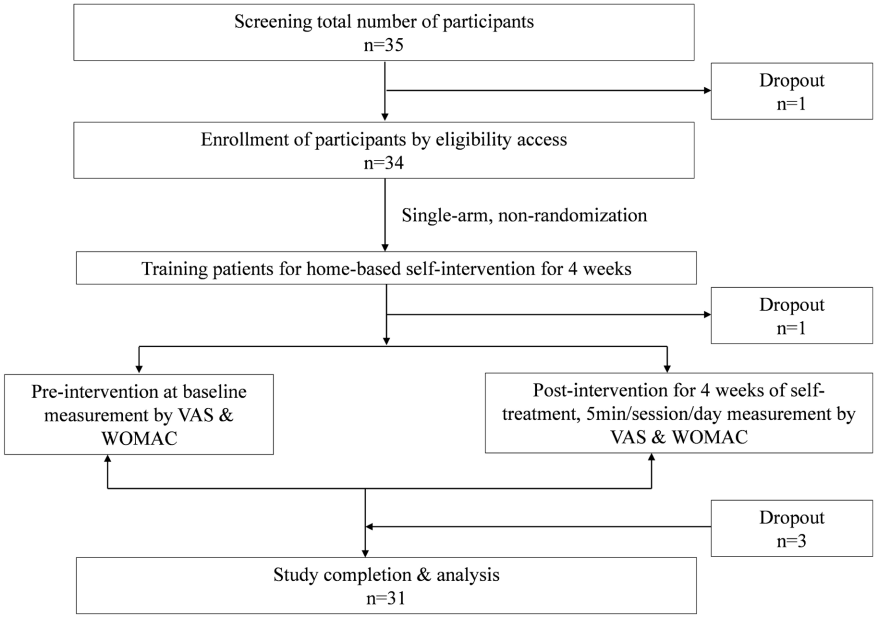

Figure 2. Flow chart of clinical trial.

Table 1. Baseline demographic characteristics of participants.

Variable		Total	Female	Male
Sex		51	39 (76.47%)	12 (23.53%)
Age (years)		57.00 ± 4.56	52.00 ± 6.82	56.00 ± 5.40
Body weight (Kg)		68.00 ± 2.90	60.00 ± 3.40	75.00 ± 4.80
Temperature (°C)		36.4.00 ± 0.11	36.2.00 ± 0.11	36.30 ± 0.25
Height (cm)		161.00 ± 4.88	160.00 ± 6.55	165.00 ± 3.55
Blood Pressure (mmHg)	Systolic	130.00 ± 2.34	125.00 ± 1.26	130.00 ± 2.42
	Diastolic	80.00 ± 2.13	80.00 ± 2.68	80.00 ± 2.09

Data were presented mean ± SD.

COVID-19 infection (n = 2) and withdrawal of consent (n = 1). Finally, 31 patients completed the four-week treatment period (Figure 1). Baseline demographic characteristics of the 34 patients are presented in Table 1. The mean (SD) age was 57.00 (4.56) years. By sex, 22 (64.7%) were female and 12 (35.3%) were male. Body weight was 60.00 ± 3.40 kg for female and 75.00 ± 4.80 kg for male.

3. Results

3.1. Primary Outcome Measured by VAS Scale after the Intervention of LICUS

Knee pain, as a primary outcome, was measured using the VAS scale before and after treatment with LICUS. As a result, four-weeks of LICUS treatment showed a significant reduction in the VAS pain score by approximately 22% – 57% compared to baseline (Table 2). Additionally, VAS pain score was measured every week, and scores were shown in Table 2. This result indicates that LICUS stimulation of the knee in patients with OA might improve pain symptoms.

Table 2. Pain score measured by VAS scale.

Time period	Baseline	Post-treatment	% difference	*p*-value
VAS score (1 week)	6.42 ± 1.03	5.10 ± 0.19*	22.92	$^{*}p < 0.05$
VAS score (2 week)	6.42 ± 1.03	4.60 ± 1.32**	33.03	$^{**}p < 0.01$
VAS score (3 week)	6.42 ± 1.03	4.10 ± 0.78**	44.11	$^{**}p < 0.01$
VAS score (4 week)	6.42 ± 1.03	3.58 ± 1.12***	56.80	$^{***}p < 0.001$

VAS, Visual Analog Scale; Data are presented as mean ± SD. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$.

3.2. Secondary Outcome Measured by WOMAC Index after the Intervention of LICUS

The WOMAC is widely used as a disease-specific tool for assessing self-reported pain and function in patients with OA of the knee or hip. It is legitimate and

responsive to alterations in the health condition of patients with OA. According to our findings, there was a significant decrease in both the pain score ($p < 0.05$) and knee stiffness score ($p < 0.001$) as evaluated by the WOMAC index after LICUS intervention. The reduction amounted to around 51.02% for pain and 67.44% for knee stiffness, compared to the initial measurements. The functional capacity score of the knee showed a significant reduction of approximately 81.91%. Similarly, WOMAC score was measured every week, and scores were shown in Table 3.

Table 3. Secondary outcome using WOMAC.

WOMAC index (number of questions)	Baseline	Post-treatment	% difference (%)	*p*-value
Knee pain (5)	9.84 ± 3.57	5.84 ± 1.85**	51.02	**$p < 0.01$
Knee stiffness (2)	3.45 ± 1.63	1.71 ± 1.27***	67.44	***$p < 0.001$
Knee function (17)	34.81 ± 12.30	14.58 ± 9.25***	81.92	***$p < 0.001$
Total score (24) 1 week	48.10 ± 14.72	40.56 ± 2.35*	17.00	*$p < 0.05$
Total score (24) 2 week	48.10 ± 14.72	36.90 ± 1.65*	26.35	*$p < 0.05$
Total score (24) 3 week	48.10 ± 14.72	28.36 ± 2.89**	51.63	**$p < 0.01$
Total score (24) 4 week	48.10 ± 14.72	22.13 ± 10.79	73.96	***$p < 0.001$

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. Data are presented as the mean ± SD. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

4. Discussion

The main objective of this clinical investigation was to assess the efficacy of LICUS therapy in alleviating pain and enhancing functional outcomes. The patients showed significant improvement in pain relief and knee function throughout a follow-up period of four-weeks based on VAS and WOMAC pain scores. Moreover, OA of the knee is considered the fourth primary contributor to disability among women, leading to a reduction in functional capabilities and overall quality of life [21]. Furthermore, Chen *et al.* discovered a favorable linear relationship between ultrasound grading and the WOMAC overall score/pain subscale [22]. For knee OA pain, ten randomized controlled trials (645 patients) using ultrasonography demonstrated a significant improvement over placebo in knee pain and a decrease in the WOMAC score [23]. The ultrasonic grading had a favorable linear relationship with the overall score/pain subscale of the WOMAC score. Numerous studies have examined various elements of muscle function in patients with OA, including pain [24], stiffness [25], and WOMAC score [26], as well as other clinical features, including muscular strength [27]. To our understanding, limited research has explored the influence of diverse non-pharmacological interventions on the functional exercise capacity of patients, despite notable progress in this field. Research suggests that ultrasound therapy is considered safe when administered correctly to eligible patients [28].

In this clinical investigation, LICUS proved to be a valuable instrument for assessing the impact of pain treatment on functional exercise capability. The present study demonstrated that LICUS exhibited significant positive outcomes on both pain levels and functional capacity among individuals with knee osteoarthritis. Post-treatment, all evaluation parameters were significantly reduced. VAS and WOMAC scores were used to assess how the treatment period affected pain, and we discovered that after four-weeks treatment significantly improved pain scores.

Using the VAS and pain dimension of the WOMAC, we assessed the effectiveness of various treatment modalities on knee pain in the current study. Our study showed that the VAS pain score was significantly reduced after the four-week intervention compared to baseline. This study is not the first to show how nonpharmacological treatment reduces knee pain in patients with OA. The results of 17 research on OA exercise were extensively examined and integrated by the Cochrane group a total of 2562 participants [29]. Our results showed that LICUS treatment significantly improved pain compared with baseline. For those with symptomatic knee OA, this study discovered that land-based activity reduced pain in a small to moderately positive manner. Transcutaneous electrostimulation vs. sham or no specific intervention on pain in people with knee OA was the subject of a comprehensive Cochrane study by Rutjes *et al.* [30]. In comparison with sham or no intervention, electrostimulation had no evidence of a substantial benefit on knee OA pain, according to this comprehensive study. Pain is one of the most prevalent complaints and incapacitating symptoms among patients with OA. Our study also found, using the WOMAC scale, a positive link between pain intensity and disability, which is consistent with other studies' findings, and it significantly improved pain in the post-treatment group by approximately 18% compared to the pre-treatment group [31]. Owing to discomfort, fear of pain, and the belief that additional exercise could exacerbate the condition and lead to cartilage loss, worsening the already compromised function, the patients in our study protected their joints by refraining from physical activity. Additionally, our findings indicate a positive change in the pain indicators (VAS and WOMAC index) among the post-treatment group compared to the pre-treatment group. This research establishes LICUS as an effective means of alleviating pain in individuals with OA. Consequently, LICUS has the potential to bring about cost savings in healthcare for both patients and the healthcare system when addressing chronic pain conditions. Conventional treatment guidelines for knee OA typically advocate for the incorporation of exercise programs and physical therapy (PT) as integral components in managing the condition. These interventions are commonly recognized as fundamental approaches to addressing knee OA, contributing to symptom relief, enhanced functionality, and improved overall quality of life for those affected by this condition [32]. Numerous studies have demonstrated the benefits of exercise-based programs for knee OA. These programs often include a combination of aerobic exercise, strengthening exercises, flexibility training, and balance exercises.

When examining the effect sizes of these programs, they typically range from moderate to large, indicating a meaningful improvement in pain and function [33] [34]. Pharmacological treatments for knee OA, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesics, also show comparable effect sizes in pain reduction. However, it's important to note that while pharmacological treatments can provide temporary pain relief, they may not address the underlying cause of knee OA or provide long-term benefits in terms of functional improvement [35]. The lack of evidence in a particular area can indeed pose challenges for primary care providers when making referrals. Evidence-based guidelines and recommendations play a crucial role in guiding healthcare professionals in making informed decisions about patient care, including referrals [10].

Furthermore, healthcare systems may need to consider strategies to optimize the utilization of limited resources such as outpatient PT visits. This can involve prioritization protocols, triage systems, or the development of alternative care models that can provide effective interventions while reducing the strain on limited resources.

Our findings suggest that LICUS therapy may be beneficial in addition to pharmaceutical treatment and may offer patients with knee OA who are prone to drug-related adverse effects an additional choice. The results of this study have found evidence supporting the use of LICUS therapy as a beneficial treatment for patients with knee OA. According to the study, LICUS appears to be a safe option for reducing pain and enhancing physical function in these patients. However, the study has several weaknesses, including a small sample size, a short therapy duration of four-weeks, a lack of post-treatment follow-up, and the exclusion of measures related to quality of life. However, we could not determine the long-term efficacy of LICUS therapy. To draw more definitive conclusions about LICUS therapy, further research with larger sample sizes, longer treatment durations, comprehensive post-treatment follow-up, and inclusion of quality-of-life measures would be necessary. These improvements would help to address the weaknesses identified in the study and provide a more comprehensive understanding of the treatment's benefits for patients with knee OA.

5. Conclusion

In clinical trials of OA of the knee, better conformity with the recommended application of the VAS and WOMAC scoring systems, with clear reporting, should be encouraged. Therefore, LICUS provides a desirable home-use treatment choice for patients with OA pain at 1.1 MHz frequency in continuous wave mode with 1.5 W/cm^2 intensity that will be effective and safe for OA treatment in patients. Our research also suggests that LICUS induces more thermal effects that appear to be a safe option for reducing pain and enhancing the physical function of the patients.

Authors Contribution

Kyu-Jae Lee: Conceptualization; methodology, Project administration; Writ-

ing—review and editing, Funding acquisition. **Md. Habibur Rahman**: Writing—original draft preparation; software; formal analysis; data curation. **Yeon-Gyu Jang**: Writing—original draft preparation; Data curation. **Johny Bajgai**: Formal analysis; Writing—review and editing. **Subham Sharma:** Writing—review and editing. **Kchorng Vira**: Writing—review and editing. **Abdul-Nasir Sofian**: Writing—review and editing. **Seong Hoon Goh**: Writing—review and editing. **Yundeok Kim**: Writing—review and editing. **Cheol-Su Kim**: Methodology; Writing—original draft preparation; software; resources; Writing—review and editing; Visualization; Supervision. **Doo-Sup Kim**: Writing—review and editing. All the authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Ethical approval was granted by the Institutional Review Board of Wonju Severance Christian Hospital, Yonsei University, Wonju, Republic of Korea (IRBN CR222008).

Conflicts of Interest

The authors declare no conflicts of interest

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Abbreviation

BMI	Body Mass Index
CUS	Continuous Ultrasound
LICUS	Low-Intensity Continuous Ultrasound
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
OA	Osteoarthritis
PT	Physical Therapy
PUS	Pulsed Ultrasound
VAS	Visual Analogue Scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index