LIPUS Setting and Combined Effect With Therapeutic Exercise for Knee Osteoarthritis: A Systematic Review

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Research

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Abstract

[PURPOSE] Knee osteoarthritis (OA) is a chronic progressive disorder characterized by pain and decreased joint function. In the conservative treatment for the knee OA, the physiotherapy is known to be a common intervention. Recently, low-intensity pulsed ultrasound therapy (LIPUS) which has an effect on knee pain of knee OA has been used with therapeutic exercise. However, the combined effect of LIPUS with therapeutic exercise did not have enough evidence.

This study was conducted to assess both setting off the LIPUS and combined effect of the therapeutic exercise in the Knee OA.

[METHODS] PubMed, PEDro, CENTRAL were searched for RCTs on published before September 2019. The irradiation intensity, irradiation site, and treatment period of LIPUS were examined. Meta-analysis was performed to analyze the short and long term combined effect which was LIPUS with therapeutic exercise on the VAS score. Statistical calculations of both LIPUS with therapeutic exercise group and only therapeutic exercise group were compared from detailed data of the all eligible studies.

[RESULTS] Seven RCTs were eligible. Both irradiation intensity and site were varied. Three RCTs were included in the meta-analysis, involving a total of 210 knees. There was no significant improvement in pain in the LIPUS with therapeutic exercise (LIPUS) group compared with the therapeutic exercise group in short-term (MD; -6.86, 95% CI; -18.70 to 4.99 , I² = 74%, heterogeneity: P = 0.02) and long-term (MD; -16.01 95% CI; -32.03 to 0.01, I² = 82%, heterogeneity: P = 0.004) effects.

[CONCLUSIONS] We did not find consistent evidence of the effects of combined to LIPUS and therapeutic exercise for Knee OA. Because, selected trials were varied in intensity and irradiation site and treatment durations, which might contribute to the existence of heterogeneity. Furthermore, there were few RCTs that resulted in knee joint function.

The LIPUS combined therapeutic exercise found no significant decrease the knee pain than therapeutic exercise. Therefore, RCTs were recommended by well-designed intensity and irradiation site.

Background

Low intensity pulsed ultrasound therapy (LIPUS) is a type of ultrasound therapy that uses a low intensity pulsed wave to stimulate for the fracture to promote bone union. There have been positive reports on the effect of LIPUS on bone union[1-3], but there have also been negative reports in the recent systematic review that it has no effect on bone healing[4, 5]. Therefore, the effect of LIPUS on fracture treatment will need to be discussed. Other effects of LIPUS, such as reduced inflammation[6], improved soft tissue microcirculation[7], and increased expression of vascular endothelial growth factor (VEGF)[8] have also been reported. Furthermore, several studies have reported that efficacy of LIPUS on knee osteoarthritis (knee OA)[9].
Knee OA is the most common articular disorder characterized by pain and decreased function. Primary knee OA contracted by chronic mechanical stimulation in the aging begins from 50 ~ 60 years old. In the United States, approximately 14 million people have been reported to have symptomatic knee OA[10]. In addition, because knee OA is a chronic progressive disorder, patients with severe symptoms often undergo total knee arthroplasty (TKA). However, about 20% of patients were not satisfied with TKA [11]. Also, compared with conservative treatment, serious adverse events have been reported with TKA [12], and TKA does not always yield the expected results. In addition, about 20% of the knee OA undergo to the TKA [13]. Therefore, effective conservative treatment is expected to prevent of knee OA.

Conservative treatment of knee OA often includes physical therapy, orthosis, and therapeutic exercise, which is recommended in guidelines [14, 15]. Ultrasound therapy, a type of physical therapy, is also often used in clinical practice because it improves knee OA pain [16] and increases range of motion[17] by using thermal and non-thermal mechanisms (mechanical effects). Recent systematic reviews and meta-analyses suggest that LIPUS is also effective in improving knee function[9] and that pulsed wave ultrasound is superior to continuous wave of it in improving function[18]. However, although physical therapy and therapeutic exercise are often used in combination in clinical setting, the efficacy of LIPUS treatment in combination with therapeutic exercise for knee OA has not been verified and remains controversial. In addition, the irradiation intensity, irradiation site, and type of outcome measures for LIPUS therapy have not been sufficiently examined in the literature.

Therefore, the aim of this study was to conduct a systematic review and meta-analysis of combination effects of LIPUS with therapeutic exercise, and to investigate for the parameters of LIPUS such as irradiation intensity, site, and type of outcome measures.

**Methods**

The selection of evidence, risk of bias assessment, and meta-analysis were presented according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [19].

All available years of data in PubMed, Physiotherapy Evidence Database (PEDro), and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for potential references. The search strategy used free text word retrieval and subject headings adapted for each database as well as relevant key words such as “ultrasound therapy” and “knee osteoarthritis” with the filter for article type set on “randomized controlled trial (RCT).” The search was conducted until September 2019.

All abstracts identified by electronic database searching were screened by two reviewers to exclude ineligible references. The remaining full articles were then retrieved and screened again for relevance.

The inclusion criteria are as follows:

(1) Randomized controlled trials

(2) Patients with knee osteoarthritis
(3) Studies containing at least one group using LIPUS as an intervention

(4) English literature.

The exclusion criteria are as follows:

(1) Animal studies

(2) Abstract, letter, review, systematic review/meta-analysis, or case report

(3) Non-English literature.

The selected literature was reviewed and evaluated critically by two independent reviewers. The methodological quality assessment was conducted applying the Cochrane Collaboration's tool for assessing risk of bias[20].

Visual analogue scale (VAS) scores of pain on short and long term were used as outcomes in the meta-analysis. Reviewers extracted all relevant data separately. The extracted and pooled data included first author, year of publication, number of patients, LIPUS intervention duration, observation period, radiation intensity, radiation site, VAS scores, and type of therapeutic exercise.

Meta-analysis was performed using the software package RevMan 5.3, for comparison between LIPUS combined with therapeutic exercise and therapeutic exercise only. Statistical calculations were performed for all studies of interest using detailed LIPUS combined with therapeutic exercise and LIPUS and therapeutic exercise data. The LIPUS group (LIPUS and therapeutic exercise) and the therapeutic exercise group (Therapeutic exercise only) were compared using a random effects model[21], significance was considered at P < 0.05. The reliability of the statistic is 95% (confidence interval; CI) was calculated.

Statistical heterogeneity was assessed using $I^2$ statistic[22]. Using a random effects model[11], significance was considered at P<0.05.

RESULTS

In total, 173 potential records were identified through database searches, and 125 abstracts remained after deletion of duplicate records. The abstracts were then reviewed and preliminary assessed, followed by an assessment of the eligibility of 15 full-text articles[23-37]. Of the 15 cases, seven[31-37] met the selective criteria (Figure 1) and the other eight[23-30] were excluded. These eight articles were not eligible for intervention. In addition, three [31,34,35] of the seven articles were used for meta-analysis.

The basic characteristics of included studies are shown in Table 1. The irradiation intensity was 40 ~ 500 mW/cm$^2$, and there was a variation among studies. There was also variation among studies in the area of irradiation, including the medial and lateral cleft MCL, popliteal region, and pain site. Few reports of knee joint function such as muscle strength and range of motion were observed. Figures 2 and 3 show the "risk of bias" assessment for individual studies. Selective bias is unclear because all studies failed to
confirm pre-registered outcomes. In one study, the risk of bias increased because patients were not blinded.

We evaluated the efficacy of LIPUS combined with therapeutic exercise for pain compared with therapeutic exercise only, by synthesis of three trials. Pooled VAS score did not demonstrate a short-term effect (MD; -6.86, 95% CI; -18.70 to 4.99 points, I² = 74%, heterogeneity: P = 0.02) and a long-term effect (MD; -16.01, 95% CI; -32.03 to 0.01 points, I² = 82%, heterogeneity: P = 0.004) for pain relief with LIPUS combined with therapeutic exercise (Fig 3.4).

**Discussion**

This systematic review focuses on the efficacy of LIPUS in patients with knee OA. As a result, there were seven studies related to knee OA and LIPUS, and there was the dispersion between studies on the irradiation intensity, irradiation site, and treatment period of LIPUS. Three RCTs combined LIPUS and therapeutic exercise. We conducted a meta-analysis to combined effect of LIPUS and therapeutic exercise. As the result, the desensitization effect by the combined use of LIPUS and therapeutic exercise was not recognized.

In a previous meta-analysis, the analgesic effect of LIPUS on knee OA was observed[18]. However, previous studies have included RCTs combining LIPUS with therapeutic exercise. Therapeutic exercise for knee OA is effective in relieving pain in systematic review[38]. Therefore, in previous studies, the effect of LIPUS may have been masked by the effect of the pain relief of therapeutic exercise, and it has not been sufficiently examined whether the effect of LIPUS is more effective than therapeutic exercise alone. As a result of verifying the combined effect of LUPUS and therapeutic exercise, the effect of LIPUS was not recognized, and the analgesic effect of LIPUS could not be clarified. The possible causes were that therapeutic exercise was more effective than LIPUS and that there were problems with the protocol and outcome of LIPUS. Others included anterior, medial, and lateral parts of the knee, medial collateral ligament, pes anserinus, popliteal, lateral joint space, painful areas, and unknown. Therefore, there are varied the irradiation site among the studies. In some studies reporting negative effects of LIPUS, the site of irradiation was not uniform.

Irradiation intensity ranged from 40 to 500 mW/cm², with variations among studies[30-36]. There are a large number of RCTs with no evidence of radiation intensity. However, only Jia et al. adjusted the irradiation intensity at 120 mW/cm² referring to a previous study[39] in which the effect of LIPUS was clarified from animal experiments. Previous studies in this animal experiments have reported a reduction in inflammatory mediators and in joint effusion. Therefore, a setting of the irradiation intensity of 120 mW/cm² may be effective.

There are four studies which set two week treatment durations, and three studies which set eight week treatment durations.
There are clarified only short term effects of treatment, because knee OA is chronic and progressive musculoskeletal disorder. And animal experiments have shown that LIPUS significantly suppresses inflammatory mediators and joint edema even after 8 weeks of treatment. Consideration should be given to setting the duration of treatment, as the length of treatment may affect the response to treatment.

Many of the outcomes of the selected RCTs confirmed reports of pain, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and gait. Knee OA has been reported to decrease gait function with pain and the knee function[40]. However, there are few RCTs that outcome the knee functions such as muscle strength and range of motion, and the effect of LIPUS on the knee function has not been fully understood. Therefore, further reports are needed to RCTs were recommended with well-designed intensity and irradiation site.

There is no clear evidence regarding the number of LIPUS interventions and the duration of LIPUS intervention. The analgesic effect of LIPUS could not be confirmed. However, there is a variation in irradiation intensity, irradiation site, and period between studies, so that the possibility of a difference in pain relief effect cannot be denied. Second, differences in the intensity, location, and duration of radiation between studies may have resulted in differences in pain relief. It is necessary to verify the combined effect of therapeutic exercise with outcome other than intensity, site, duration and pain.

There are several limitations in this study.

First, the intensity and type of therapeutic exercise in the three RCTs selected for the meta-analysis were different and high methodological heterogeneity. Second, the number of RCTs is small and publication bias cannot be assessed.

**Conclusion**

The desensitization effect by the combined use of LIPUS and therapeutic exercise could not be recognized. This was thought to be due to variations in the irradiation site and intensity settings. In addition, there are few studies in which changes in the structure of the knee joint are considered as an outcome, and further studies are expected.

**List Of Abbreviations**

CENTRAL Cochrane Central Register of Controlled Trials

Knee OA Knee osteoarthritis

LIPUS Low intensity pulsed ultrasound

PEDro Physiotherapy Evidence Database

PRISMA The Preferred Reporting Items for Systematic Reviews and Meta-analyses
Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Availability of data and materials
All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests
The authors declare that they have no competing interests.

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Authors' contributions
Conceived ideas or experimental design: MK, SK.
Searching: MK and SK.
Data analysis and interpretation: MK, YO, and SK.
Wrote the manuscript: MK.
Supervised the study and edited the manuscript: YO, HK, and SK.

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References

2018;34(3):652-659.


Tables
Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.