

## Review Article

# Effect of ultrasound therapy for knee osteoarthritis: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials

Changjie Zhang<sup>1\*</sup>, Jie Shi<sup>2\*</sup>, Chunjiao Zhu<sup>1</sup>, Tian Xiang<sup>1</sup>, Zhongjie Yi<sup>3</sup>, Ying Kong<sup>1</sup>

<sup>1</sup>Department of Rehabilitation, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, P.R. China; <sup>2</sup>Department of Rehabilitation, Changsha Central Hospital, Changsha, Hunan 410004, P.R. China; <sup>3</sup>Department of General Surgery, The Third Xiangya Hospital, Central South University, Changsha, Hunan 410013, P.R. China. \*Equal contributors.

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**Abstract:** Objective: To perform a meta-analysis of randomized, double-blind, placebo-controlled clinical trials to separately assess the effect of continuous ultrasound (US) therapy and pulsed ultrasound therapy with low frequency for decreasing pain and improving physical function on people with knee osteoarthritis. Data sources: A systematic review (to April 2015) is conducted without language limits in PubMed, OVID and Medline database. Study selection: All trials were selected for adequate randomization, double-blind, follow-ups and control group involving patients diagnosed knee OA. Data extraction: 6 trials were excluded for the reasons below: (1) Without control. (2) Incomplete data. (3) Single blind. Data synthesis: After reviewed by Pubmed, OVID and Medline database, six clinical trials of 417 patients were included. Compared to sham US, continuous US reduced pain on a 10 cm visual-analogue-scale (VAS) [Standardized Mean Difference (SMD) (95% confidence interval (CI)) = -0.58 (-0.91, 0.25), P = 0.0006], while pulsed US reduced pain [SMD 95% confidence interval (CI) = -1.06 (-1.46, -0.65), P<0.001]. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscale score of continuous US were improved [SMD 95% confidence interval (CI) = -3.74 (-8.16, -0.67), P = 0.10] compared to sham US. Conclusion: These results demonstrated that both continuous and pulsed Ultrasound therapy could efficiently reduce pain and improve physical function in people diagnosed with knee osteoarthritis. The pulsed US seemed more effective in these aspect to improve patients' life quality.

**Keywords:** Osteoarthritis, knee, ultrasound, therapy

## Introduction

Osteoarthritis (OA) is a concerning problem nowadays, especially in the elders. It is a group of heterogeneous diseases caused by the failure of integrity of articular cartilage and pathological changes of subchondral bone joint edge plate lesions [1, 2]. OA manifested in joint pain, tenderness, stiffness, joint swelling, restricted movement and joint deformity and mainly age-related, owing to low reaction for chondrocytes on growth factors, mitochondrial dysfunction and oxidative stress [3], etc. Though the pathogenesis of OA is not completely clear, the key segment is the unbalance of proliferation and differentiation of chondrocytes. However, more factors proved relevant to OA, including erythro-

cyte sedimentation rate (ESR), Gel-200, C-reactive proteins (CRP), GDF-5, cross-linked hyaluronates by some studies recently [4-7].

OA therapy includes physiotherapy, NSAIDs, glucosamine, chondroitin sulfate, exercises, and prosthetic replacement of joint. While ultrasound is frequently used in the treatment of patients with OA in most countries, many clinical trials and basic researches showed that ultrasound was effective in alleviating the sufferings of the patients or animals diagnosed with knee OA [8-11]. However, studies either focused on the mechanism and effect of the continuous US, or concentrated on those of the pulsed US. Still the effect of ultrasound therapy is controversial. Especially there was no discus-

# Ultrasound therapy for osteoarthritis

**Table 1.** Characteristics and references of excluded studies

| Study                       | Treatment   | Reason for exclusion |
|-----------------------------|---|----------------------|
| Sánchez et al. 2012 [28]    | Ultrasound  | Without control      |
| Cetinet et al. 2008 [29]    | Hot Pack vs Short-Wave vs Diathermy vs Ultrasound vs and TENS | Single blind         |
| Mascarin et al. 2012 [30]   | Kinesiotherapy vs ultrasound vs electrotherapy                | Not with placebo     |
| Luksurapan et al. 2013 [31] | Phonophoresis of Piroxicam vs Ultrasound                      | Not with placebo     |
| Kuroki et al. 2008 [32]     | Ultrasound  | Without control      |
| Falconer et al. 1992 [33]   | Ultrasound  | Incomplete data      |

sion and comparison for the effect of continuous US and pulsed US separately. To systematically reveal the effect of US, we searched three databases as far as possible, up to April, 2015, to evaluate the efficacy of ultrasound in improving patients' life quality with OA.

## Materials and methods

### Literature search

The PUBMED, the OVID, and Medline, these three database were searched from 2005, up to April 2015 to view all randomized, controlled and double-blind clinical trials (RCTs) conducted on OA patients with the treatment of US, used the following medical subject headings: ("osteoarthritis, knee" [MeSH Terms] OR ("osteoarthritis" [All Fields] AND "knee" [All Fields]) OR "knee osteoarthritis" [All Fields] OR ("knee" [All Fields] AND "osteoarthritis" [All Fields])) AND ("ultrasound" [All Fields] OR "ultrasound" [All Fields] OR "ultrasonic" [MeSH Terms] OR "ultrasonic" [All Fields]). No language limit is included.

### Data collection and quality assessment

Three reviewers independently assessed trials according to the titles, abstract, full-texts from databases and further information through contact to the authors. Disagreement is resolved by consensus. The trials concealment of treatment allocation, the double-blinding and completeness of outcome analysis were examined to assess the quality of the trials.

### Inclusion and exclusion criteria

All selected trials were reached the inclusion criteria: (1) study groups received the US treatment; (2) adequate randomization; (3) double-blinding; (4) adequate follow-ups; (5) control groups. All patients involved were diagnosed

knee OA. Trials conducted that study groups with intervention of continuous US or pulsed US, and control groups with placebo or empty control. Trials with physical intervention both in US group and controlled group were also included. Exclusion criteria included: (1) violated the inclusion criteria; (2) patients with diabetes, rheumatoid arthritis or other osteoarticular diseases; (3) other interventions involved except for US and exercises.

### Statistical analyses

The meta analysis used Review Manager (Rev-Man Version 5.2 Copenhagen). Inverse-variance fixed or random effects model was used to calculate the weighted mean difference (WMDs). If mean difference was high, standard mean difference (SMDs) is calculated. Random models used only when large heterogeneity occurred. The outcome of the study was calculated at the end of trial and at the baseline. The 95% confidence interval (CI) was calculated and a Z test was performed with  $P < 0.05$  deemed statistically significant. Heterogeneity among trials was assessed with  $\chi^2$  test with significance set at  $P < 0.10$  and an inconsistency test ( $I^2$ ) when inconsistency ( $I^2$ )  $> 50\%$  denoted large heterogeneity.

## Results

After search 305 citations, 30 full text articles were examined for further information. 12 trials containing US as treatment intervention in study group and only six randomized, double-blind trials were included in our meta-analysis. 6 trials were excluded for non-placebo control design (4), no double-blind design (1) and insufficient information (1). These 6 trials were excluded for the reasons as in the **Table 1**.

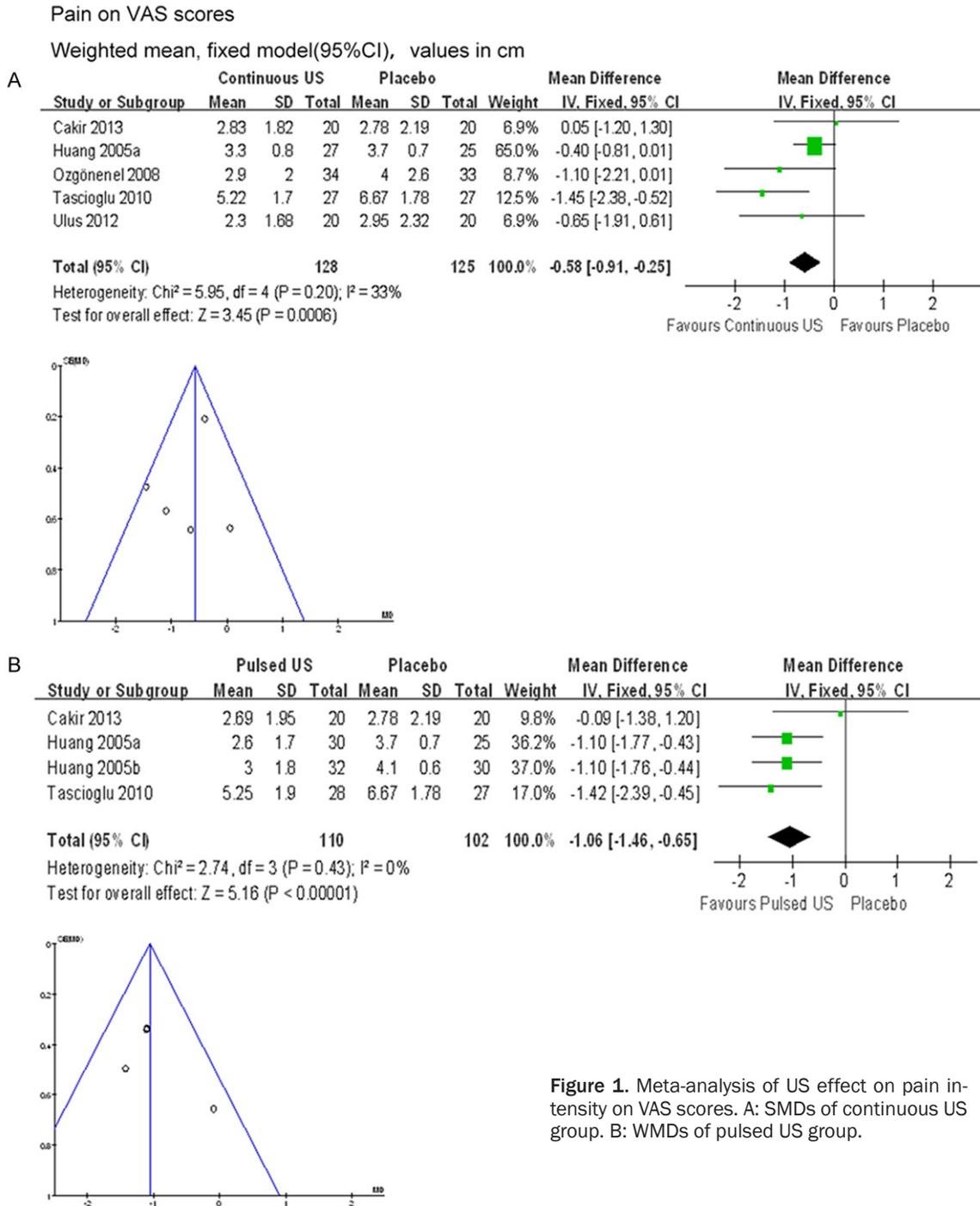
English journals delivered the selected 6 trials in articles. All were randomized, double-blind with the US energy 1 MHz, including 409

## Ultrasound therapy for osteoarthritis

**Table 2.** Characteristics of selected trials of US

| Study                      | Intervention group  | Control group   | Treatment duration      | Joint | Follow-upadequate | Outcomes measurements   | Patients Randomization (continuous US /pulsed US/Placebo) | Mean age | Women%  |
|----------------------------|---|---|-------------------------|-------|-------------------|---|---|----------|---------|
| ÖZGÖNENEL et al. 2009 [12] | Peterson. 250 US device; continuous mode; frequency 1 MHz; intensity 1 W/cm <sup>2</sup>  | Sham ultrasound (applicator disconnect device)                                | 5 times a week for 2 wk | knee  | yes               | VAS, WOMAC and 50 meter walking time  | 67 (34/33) (continuous US/Placebo)                        | 54.8     | 81      |
| Cakir et al. 2014 [13]     | Sonoplus. 190 US device (1) continuous US; frequency 1 MHz; intensity 1 W/cm <sup>2</sup> (2) pulsed US; same frequency and intensity on 1:4 pulse ratio              | sham ultrasound (power switch off)  | 5 times a week for 2 wk | knee  | yes               | VAS, WOMAC, 20-m walking time.  | 60 (20/20/20) (continuous US/pulsed US/Placebo)           | 57.4     | 78      |
| Tascioglu et al. 2010 [14] | Sonopuls. 434 US device (1) continuous US; frequency 1 MHz; intensity 2 W/cm <sup>2</sup> (2) pulsed US same frequency and intensity on 1:4 pulse ratio               | sham ultrasound (without delivering any Output)                               | 5 times a week for 2 wk | knee  | yes               | VAS, WOMAC  | 82 (27/28/27) (continuous US/pulsed US/Placebo)           | 60.5     | 65      |
| ULUS et al. 2012 [15]      | Sonopuls. 434 US device, continuous US; frequency 1 MHz; intensity 2 W/cm <sup>2</sup>  | sham ultrasound (no energy delivered and applicator disconnected from device) | 5 times a week for 3 wk | knee  | yes               | VAS, WOMAC, 50-m walking time, LSI, HAD (anxiety and depression subscore)                 | 40 (20/20) (continuous US/Placebo)                        | 60.5     | unclear |
| Huang et al. 1. 2005 [16]  | Sonopulus. 590 (1) continuous US; frequency 1 MHz; intensity 1.5 W/cm <sup>2</sup> (2) pulsed US; frequency 1 MHz; intensity 2.5 W/cm <sup>2</sup> on 1:4 pulse ratio | Without US  | 3 times a week for 8 wk | knee  | yes               | VAS, Knee ROM, Lequesne index (LSI), ambulation speed (AS), and muscle peak torques (MPT) | 90 (30/30/30) (continuous US/pulsed US/Placebo)           | 62.0     | 76      |
| Huang et al. 2. 2005 [17]  | Sonopulus. 590, pulsed US, frequency 1 MHz; intensity 2.5 W/cm <sup>2</sup> on 1:4 pulse ratio  | Without US  | 3 times a week for 8 wk | knee  | yes               | VAS, Knee ROM, ambulation speed (AS), and muscle peak torques (MPT), Lequesne index (LSI) | 70 (35/35) (pulsed US/Placebo)                            | 65.0     | 81      |

# Ultrasound therapy for osteoarthritis



**Figure 1.** Meta-analysis of US effect on pain intensity on VAS scores. A: SMDs of continuous US group. B: WMDs of pulsed US group.

patients diagnosed knee OA by American College of Rheumatology (ACR) criteria. The mean age and gender spread of the trials were similar (Mean age varied from 54 y to 65 y, gender spread varied from 65% to 81%). The follow-ups were at least 6 months. No large heterogeneity was found in the outcome of the Visual Analogue Scale (VAS), Western Ontario and

McMaster Universities osteoarthritis index (WOMAC) scores, LSI scores in continuous US group and knee ROM ( $I^2 < 50\%$ ) without evidence of publication bias. While  $I^2 > 50\%$  in LSI scores in pulsed US group, 50 m-walking time and AS, randomized model was used. The main information of the selected 6 trials was displayed in **Table 2.**

## Ultrasound therapy for osteoarthritis

Self-reported physical function on WOMAC scores

Weighted mean, fixed model(95%CI )

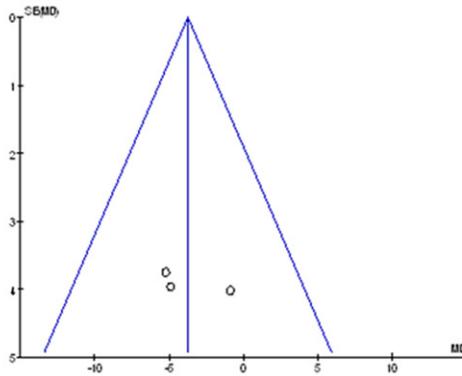
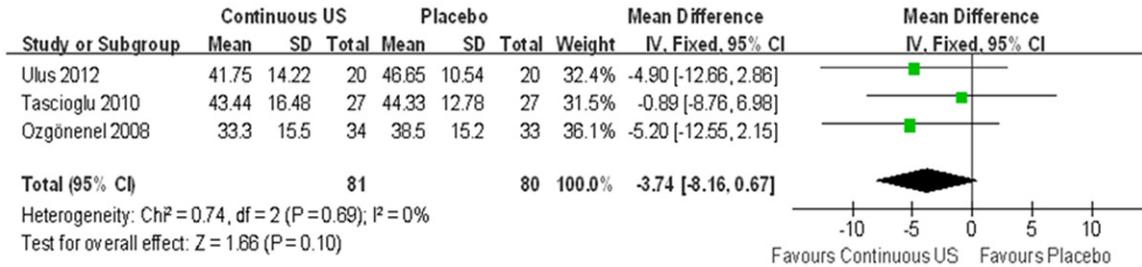


Figure 2. Meta-analysis of ultrasound effect on WOMAC scores.

ÖZGÖNENEL [12] and his colleagues conducted trials on 67 patients between 45 y and 65 y with bilateral knee OA suffering pain and limitation of activity, whose Kellgren-Lawrence scores were 2-3 on radiological evaluation and a pain score on VAS of 30 mm or more. The primary outcome measurement was a pain score on the VAS and secondary outcomes were the WOMAC and 50-m walking time at the baseline and after the treatment.

Cakir [13] and colleagues included 60 patients with bilateral knee OA radiologically in Kellgren-Lawrence grades of 2 or 3, aged 40 y to 80 y and a pain score of at least 30 mm on VAS. The outcome measurements were VAS, WOMAC, and 20 m-walking time after the treatment.

Tascioglu [14] and colleagues recruited 82 patients of bilateral knee OA between the ages of 54 y and 70 y with Kellgren-Lawrence grades of 2 or 3 and pain score on VAS of more than 50 mm. The study measured the treatment effect with pain on VAS scores and self-reported physical function on the WOMAC scores.

ULUS [15] and colleagues randomized 40 patients diagnosed with bilateral knee OA into continuous US group and placebo group. All patients were between 42 y to 75 y with VAS

score at least 20 mm, Kellgren-Lawrence grades of 2 or 3, Lequesne index score between 2-19. The outcome measurement included VAS, WOMAC and 50 m-walking time, Lequesne index, HAD anxiety and depression subscore.

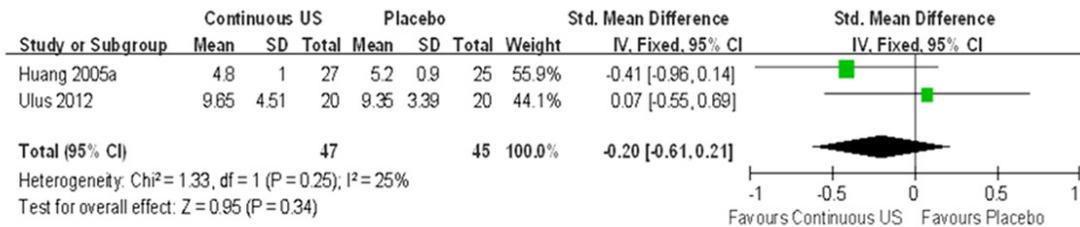
Huang [16] and colleagues included 120 patients ranged in age 42 y to 72 y with bilateral knee OA (Altman grade II) with VAS score at least 30 mm into four group: group I received isokinetic muscular strengthening exercises; group II received isokinetic exercise and continuous US; group III received isokinetic exercise and pulsed US; and group IV served as controls. In our meta-analysis, only group I to III reached our request, therefore group IV excluded. Group I served as controls and II, III as study group. VAS, Knee ROM, Lequesne index, ambulation speed, and muscle peak torques (MPT) were the main outcomes observed in study.

Another study Huang [17] with colleagues conducted on 140 subjects with bilateral knee OA (Altman grade II), with VAS score at least 30 mm, randomly assigned to four groups. Group I received isokinetic exercises; group II received isokinetic exercise and pulse ultrasound; group III received isokinetic exercise, pulse ultrasound, and intra-articular hyaluronan therapy; and group IV served as the control group. We

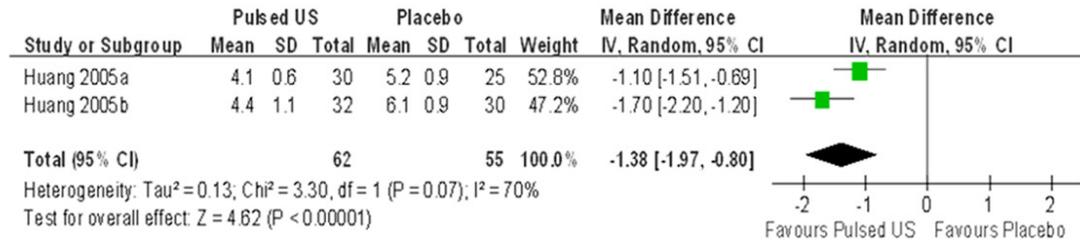
# Ultrasound therapy for osteoarthritis

LSI

## A Standard mean, fixed model(95%CI)



## B Weighted mean, randomized model(95%CI)



**Figure 3.** Meta-analysis of US effect on LSI. A: SMDs of continuous US group, fixed model. B: WMDs of pulsed US group, randomized model.

only selected group I and II according to our analysis with group I as controls. The outcomes measurements included VAS, Knee ROM, Lequesne index, ambulation speed, and muscle peak torques (MPT).

### Effects on joint pain

We compared the effect of continuous US to placebo and pulsed US to placebo separately on two tree diagrams as **Figures 1** and **2** below. With fixed model, our analysis found a statistical significant difference regarding reduction of pain both in continuous US and pulsed US group from baseline. On VAS score, in continuous US group the pain was reduced of -5.8 mm (95% CI -9.1 to -2.5,  $P = 0.0006$ ) (**Figure 1A**) and in pulsed US group the pain reduction was -10.6 mm (95% CI -14.6 to -6.5,  $P < 0.00001$ ) (**Figure 1B**). No significant heterogeneity were detected both in continuous US ( $I^2 = 33\%$ ) and pulsed US group ( $I^2 = 0\%$ ).

### Effect on self-reported physical function

Four trials included self-reported physical function measurements. Three trials observed WOMAC scores in continuous US group. Two pulsed US groups and two continuous US groups used

Lequesne Severity Index (LSI). And one trial used WOMAC scores and LSI both. A significant difference was found in the fixed model analysis according to the reduction of WOMAC scores as shown in the **Figure 2**. The difference of WOMAC scores between groups was statistically significant with reduction of -3.74 (95% CI -8.16 to -0.67,  $P = 0.10$ ). No heterogeneity was found with the  $I^2 = 0\%$ .

In the fixed model analysis in continuous US groups of LSI, the difference between groups was not significant with decreased of -0.20 (95% CI -0.61 to 0.21,  $P = 0.34$ ) in **Figure 3A**. Since the mean difference between those two trials was high, SMDs was used. No heterogeneity was found with the  $I^2 = 25\%$ . In the pulsed US groups, a randomized model was used because of the large heterogeneity ( $I^2 = 70\%$ ). An obvious decrease was found with -1.38 (95% CI -1.97 to -0.80,  $P < 0.00001$ ) in **Figure 3B**.

### Effects on joint ROM (Range of Motion)

Two trials with pulsed US were extractable with outcome measurement used the knee ROM after intervention. The fixed model analysis displayed knee ROM was statistically significant with increased of  $7.4^\circ$  (95% CI 1.56 to 13.24,  $P$

# Ultrasound therapy for osteoarthritis

## Knee ROM

Weighted mean, fixed model(95%CI)

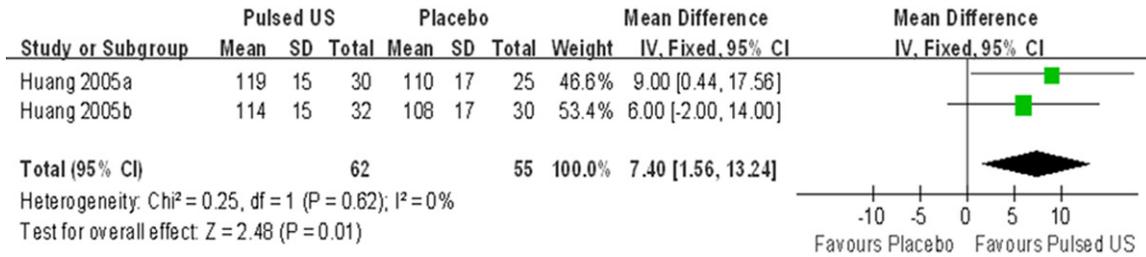


Figure 4. Meta-analysis of ultrasound effect on knee ROM (Range of Motion).

## 50m-walking time

Standard mean, randomized model(95%CI)

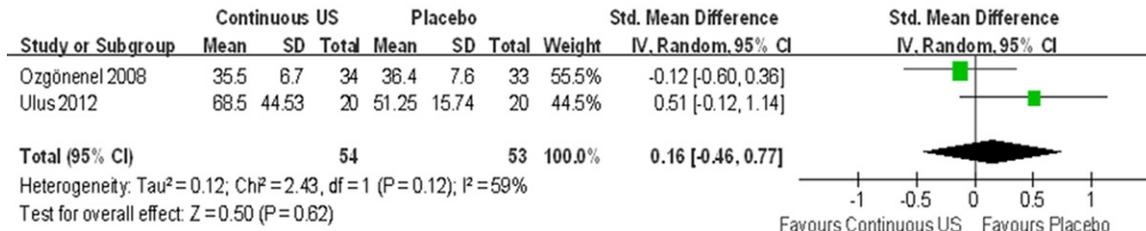


Figure 5. Meta-analysis of ultrasound effect on 50 m-walking time (continuous US).

## AS(Ambulation speed)

Standard mean, randomized model(95%CI)

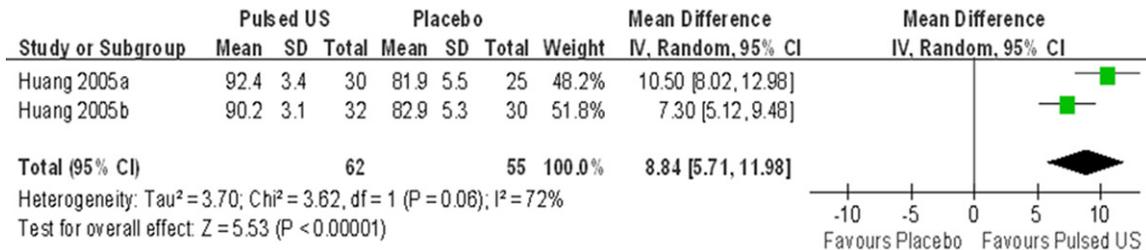


Figure 6. Meta-analyses of ultrasound effect on AS (Ambulation Speed) (pulsed US).

= 0.01) as shown in the **Figure 4**. Heterogeneity was not detected with I<sup>2</sup> = 0%.

### Effects on walking performance

Two trials with continuous US treatment assessed walking performance by 50 m-walking time and one trial assessed by 20 m-walking time. We compared the two trials calculated SMDs and used randomized model in **Figure 5**. The figure revealed no significant decreasing of walking time with 0.16 (95% CI -0.46 to 0.77, P = 0.62). Heterogeneity was obvious with I<sup>2</sup> = 59%.

### Effects on AS (ambulation speed)

Two trials with pulsed US treatment were reported assessed AS (Ambulation Speed) as an outcome measurement. A significant heterogeneity was detected with I<sup>2</sup> = 72%. Our randomized model analysis revealed a statistically significant increase of AS 8.84 (95% CI 5.71 to 11.96, P<0.00001) in the two trials as the **Figure 6** displayed.

### Discussion

This meta-analysis demonstrated that ultrasound of 1 MHz were effective in reducing pain

intensity and WOMAC scores meanwhile increasing the knee ROM and the AS. In aspect of 50 m-walking time and LSI, no obvious reduction was shown. In overall effect, ultrasound was efficient in reducing pain and improving physical function.

This meta-analysis used fixed models to assess the outcome values, and randomized models used when large heterogeneity occurred [18-21]. A systematic literature review from three authorized databases were used in our design. This analysis supported the conclusion of previous meta-analysis from Sánchez [22] published in 2010. Much different from the previous analysis were that our meta-analysis included three articles from 2010 to 2013 and excluded some articles the previous analysis used but violated the double-blind, randomized rules or with incomplete data. Another big change was that our meta-analysis discussed the continuous US effects and pulsed US effects by separate comparison with control groups from the post-treatment, which implied more meaningful thoughts. However, some problems remain to be solved. Firstly, a majority of our studies didn't evaluate the effects in the follow-up time. Therefore, we can't figure out how long did the effect last and whether it had adverse effects. Secondly, not all trials included same outcome measures, which led to partial calculation of some trials for conclusion and some bias. Finally, factors like different doses and treatment durations caused bias.

From the VAS score and LSI measurements, we found pulsed US probably more effective compared to the continuous US. Ultrasonic therapy was widely known for its thermal effect, mechanical effect, micro massage effect, cavitation and acoustic streaming. Recently, the proliferation of chondrocytes, Schwann cells, and bone regeneration was confirmed to be promoted by ultrasound [23-25]. But the promoting effect can't explain the preferable outcomes in pulsed US group. The core mechanism of osteoarthritis was the chondrocytes degeneration. And so far, a few literatures claimed that continuous US brought more thermal effect than pulsed US at the same intensity and frequency. We rationally assumed the mechanism could be that the pulsed cycle suited the proliferation rates more appropriately with the mechanical effect like micro massage and less thermal

effect. We can judge from the fact that in our meta-analysis that continuous US had less effect in improving patients' life quality than pulsed US. Firstly, the difference may be in relationship with the micro massage. Micro massage could increase the permeability of the chondrocytes membrane, accelerate the rates of diffusion across the chondrocytes membrane, improve the metabolism of chondrocytes and change the ischemia and hypoxia of cell so as to increase the chondrocytes regeneration. Secondly, the thermal effect probably counts against the chondrocytes proliferation. Some basic research discovered excessive heat would damage the chondrocytes and cellular matrix [26, 27]. But all the research discussed the effect with the energy higher than 15 W/cm<sup>2</sup>, the thermal damages of low energy require to be researched. Last but not the least, thermal effect includes dilating the blood vessels, accelerating the blood flow and reducing the pain. Therefore, continuous US is still effective in reducing pain through the VAS scores. The hypothesis need more laboratory record supports. It could be our next design to reveal the mechanism of the effect on osteoarthritis between the pulsed US and continuous US and to confirm our thought.

### Conclusion

In conclusion, our meta-analysis confirmed that both continuous US and pulsed US were effective in releasing pain intensity and improving physical function. Therefore, it improves patients' life quality. Judging from our diagrams, Pulsed US occurs to have more efficient results than continuous US through the joint pain release and self-reported physical function. However, the effect lasting time and the mechanism why pulsed US had better effect than continuous US are still required more study data to be discovered.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Ying Kong, Department of Rehabilitation, The Second Xiangya Hospital, Central South University, 139 Renmin Middle Road, Changsha 410011, Hunan, P.R. China. Tel: +0086+13975806768; E-mail: kongying15-02@126.com

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## Ultrasound therapy for osteoarthritis

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