

Ultrasound Combined Transcutaneous Electrical Nerve Stimulation versus Phonophoresis of Piroxicam on Symptomatic Knee Osteoarthritis: a Randomized Double-Blind, Controlled Comparative Study

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อัลตราซาวด์ร่วมกับการกระตุ้นเส้นประสาทเปรียบเทียบกับอัลตราซาวด์โฟโนโฟเรซิส ด้วยยาไพโรคซิแคมในภาวะปวดเข่าจากข้อเข่าเสื่อม: การศึกษาทดลองชนิดเปรียบเทียบ โดยวิธีสุ่มและมีการปกปิด

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ABSTRACT

Objective: Aims to compare effects of ultrasound combined transcutaneous electrical nerve stimulation (UltraTENS) and phonophoresis (PhP) in mild- to moderate degree of symptomatic knee OA.

Study design: A randomized double-blind, controlled comparative study.

Setting: Department of Rehabilitation Medicine, Faculty of Medicine, Chulalongkorn University

Subjects: Sixty-one patients (55 women and 6 men), ages 51 to 80 years (mean = 63.4±8.1), visual analog scale (VAS) of knee pain intensity ranged from 50-90 mm (mean=66.1) and Kellgren-Lawrence score of grade I-III, were randomly allocated into the Ultra TENS group and the PhP groups (n=31 and 30, respectively).

Method: The UltraTENS group received a combined ultrasound with TENS and a non-drug gel, whereas the PhP group received an ultrasound with piroxicam gel and sham TENS. All patients were treated for a total of 10 sessions, consisting of five times per week and 10 min per session.

Outcome Measures: Using a double blinded procedure, the primary outcome measure was evaluated pre- and post-treatment using a 100-mm VAS. The secondary outcome was assessed using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index.

Results: The UltraTENS and the PhP groups ($p<0.001$) experienced considerable improvement in both VAS and total WOMAC

scores post-treatment. The PhP group had better pain VAS and the WOMAC scores, but these findings were not statistically significant ($p=0.70$ and 0.61 , respectively).

Conclusion: Results show that UltraTENS and PhP were effective for relieving pain and improve functionality in Kellgren-Lawrence grades I-III knee OA. There were no significant differences between groups. Both agents are recommended as effective combination methods for symptomatic knee OA treatment.

Keywords: knee osteoarthritis, pain, phonophoresis, transcutaneous electrical nerve stimulation

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บทคัดย่อ

วัตถุประสงค์: เพื่อเปรียบเทียบผลการรักษาภาวะปวดเข่าจากข้อเข่าเสื่อมที่มีระดับความรุนแรงน้อยถึงปานกลางระหว่าง UltraTENS และ PhP

รูปแบบการวิจัย: การศึกษาทดลองชนิดเปรียบเทียบโดยวิธีสุ่มและมีการปกปิด

สถานที่ทำการวิจัย: ภาควิชาเวชศาสตร์ฟื้นฟู โรงพยาบาลจุฬาลงกรณ์
กลุ่มประชากร: จำนวน 61 ราย (หญิง 55 ราย, ชาย 6 ราย), อายุอยู่ในช่วง 51 ถึง 80 ปี (ค่าเฉลี่ย 63.4±8.1 ปี), มีค่าคะแนนปวดเข่า VAS ระหว่าง 50-90 มม. (ค่าเฉลี่ย 66.1 มม.) และมีระดับคะแนน Kellgren-Lawrence 1 ถึง 3 โดยทั้งหมดได้รับการสุ่มเข้าสู่กลุ่มศึกษา UltraTENS 31 ราย และ PhP 30 ราย

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วิธีการศึกษา: กลุ่ม UltraTENS ได้รับการรักษาด้วยเครื่องอัลตราซาวด์ที่มีการกระตุ้นเส้นประสาทไปพร้อมกันโดยใช้เจลที่ไม่ผสมยาขณะทำการรักษา ขณะที่กลุ่ม PHP ได้รับการรักษาด้วยเครื่องมืออัลตราซาวด์เครื่องตัวเดียวกันกับอีกกลุ่มทดลองร่วมกับการกระตุ้นไฟฟอลอกและใช้เจลยาที่มีตัวยาไพโรคซิแคมผสมอยู่ขณะทำการรักษา ผู้ป่วยทั้ง 2 กลุ่มได้รับการรักษาครั้งละ 10 นาที, 5 ครั้งต่อสัปดาห์ รวมทั้งหมด 10 ครั้ง ผู้ประเมินไม่ทราบผู้ป่วยอยู่กลุ่มทดลองใดก่อนและหลังการทดลองผู้ป่วยจะได้รับการวัดค่าคะแนนการปวดเข่า ด้วยค่าคะแนน 100 มม. VAS และวัดค่าคะแนนการใช้งานเข่าด้วยแบบสอบถาม WOMAC

ผลการศึกษา: ทั้งสองกลุ่มมีค่าคะแนน VAS และ WOMAC ดีขึ้นอย่างมีนัยสำคัญ ($p < 0.001$) เมื่อเปรียบเทียบค่าคะแนนก่อนและหลังการรักษา เมื่อเปรียบเทียบระหว่างกลุ่มพบว่ากลุ่ม PhP มีค่าคะแนนปวด VAS และคะแนนการใช้งาน WOMAC ลดลงเฉลี่ยมากกว่ากลุ่ม UltraTENS แต่ไม่ถึงระดับที่มีนัยสำคัญทางสถิติ ($p = 0.70$ และ $p = 0.61$, ตามลำดับ)

สรุป: เครื่องมือกายภาพที่ใช้เทคนิคผสมรวมทั้ง UltraTENS และ PhP สามารถลดอาการปวดข้อเข่า และเพิ่มการใช้งานข้อได้อย่างมีประสิทธิภาพในผู้ป่วยข้อเข่าเสื่อมรุนแรงระดับน้อยถึงปานกลาง ได้ดีไม่แตกต่างกันทั้งสองกลุ่ม

คำสำคัญ: ข้อเข่าเสื่อม อาการปวด โฟโนโฟเรซิส เครื่องกระตุ้นเส้นประสาทด้วยไฟฟ้า

เวชศาสตร์ฟื้นฟูสภาวะ 2560; 27(2): 46-52.

Introduction

Knee osteoarthritis (OA) is the most common degenerative joint disease and a global healthcare burden. This disease is especially problematic in aging population due to its high prevalence and frequent association with disability.⁽¹⁻⁵⁾ Common symptoms of knee OA include pain, stiffness, decrease in range of motion (ROM), physical activity limitation and deterioration in quality of life (QOL). Several pharmacologic and non-pharmacologic strategies have been studied for pain-relief and function improvement. Recently, the American Academy of Orthopedic Surgeons (AAOS)⁽⁶⁾ published a revised version of the clinical practice guideline (CPG). This guideline recommends education, exercise and topical non-steroidal anti-inflammatory drugs (NSAIDs) for patients with symptomatic knee OA. While physical agents, including electrotherapeutic modalities, are frequently prescribed for relieving pain in physical therapy, effects of these treatments are inconclusive due to a lack of compelling evidence. Therefore, these authors recommended further research in the treatment of knee OA.⁽⁶⁾

A knee OA treatment modality that can effectively reduce pain and inflammation is needed in clinical practice. Therapeutic ultrasound (US)⁽⁷⁾ and transcutaneous electrical nerve stimulation (TENS)^(8,9) are physical modalities that have been used for decades in clinical practice. The US is frequently used with other modalities including TENS or with medication so called phonophoresis (Ph) with the aim of improving pain relief.⁽¹⁰⁾

The Ph enhances percutaneous absorption of topical drugs into a deeper tissue. A growing interest in this technique is evidenced by the performance of many such trials in recent

years.⁽¹¹⁻¹³⁾ One previous study⁽¹⁴⁾ was conducted in our setting. It reported superiority of the Ph with piroxicam (PhP) compared with a standard US for treating symptomatic knee OA. Advantages of this method include non-invasiveness, minimal gastrointestinal side effects risk, low cost and good compliance. The combination effect from both US and NSAIDs provides the therapeutic response for pain relief.

TENS is an application of electrical stimulation to reduce pain perception via a gate-control theory mechanism. The technique was proposed by Melzack and Wall in 1965.⁽¹⁵⁾ Noxious stimuli are transmitted from the periphery along small myelinated A-delta nerve and small unmyelinated C nerve fibers. According to gate control theory, non-nociceptive A-beta nerve fiber activation can inhibit noxious stimuli transmission from the spinal cord to the brain. It has been found to be effective among older populations.⁽¹⁶⁾ It is non-pharmacological, noninvasive, easy to use and has no toxicity or overdose potential. It can be used in combination with the US for reducing pain in various musculoskeletal conditions including knee OA.⁽¹⁷⁾ Nowadays US machines have a combination mode, consisting of the US and the TENS (UltraTENS). With this mode, patients simultaneously receive ultrasound waves and electrical stimulation. It is accepted and frequently used in our setting because of its convenience, good compliance and low risk.

Both the UltraTENS and the PhP are common combination techniques that aimed to efficaciously relieve pain. Interestingly, the different add-on agent for each piece of equipment offers different therapeutic effects. These effects include the anti-inflammatory consequence of NSAIDs for PhP, and the analgesic result from electrical nerve stimulation in UltraTENS. Determining which is better for knee OA pain relief is difficult. As there is no a randomized clinical trial comparing which modality is more effective for treating musculoskeletal conditions, we aim to compare the effects of both treatments on pain relief and improving functional activity in symptomatic knee OA.

Methods

Participants

This study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University (IRB no.148/55). All participants were recruited from the Department of Rehabilitation Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Each participant agreed to the protocol and provided written informed consent. Every eligible participant fulfilled the American College of Rheumatology criteria for knee OA,⁽¹⁸⁾ including grade I to III of Kellgren-Lawrence scores⁽¹⁹⁾ and a 50 mm of visual analog scale (VAS) for pain or more. Exclusion criteria included any patient with the previous UltraTENS experience, contraindications for performing the US and the TENS, other causes of knee pain (including tendinitis and bursitis), piroxicam allergies and, a history of knee surgery and/or other chronic systemic inflammatory diseases.

Study design and randomization

This study was a randomized double blinded (patient and assessor), comparative controlled trial. Several measures were taken to randomize and blind patients. All patients who met inclusion criteria were randomly allocated to two treatment groups: the UltraTENS and the PhP. To ensure successful randomization, a computer-generated, permuted block of four schedule assignments was prepared in well-sealed, sequentially numbered, opaque, tamper-proof envelopes. Study gels

were concealed in identical packaging according to the randomized list. The same therapist treated both groups with the same ultrasound machine. The treatment technique was not revealed to patients. Skin preparation, electrode placement, stroking technique and equipment appearance were identical. The UltraTENS group received US with a standard non-drug gel and TENS, whereas the PhP group received US with piroxicam gel and sham TENS. The doctor, who was one of our authors, was assigned as an assessor and blinded to a randomized sequence.

Treatment procedures

Combination of ultrasound therapy and TENS stimulation (UltraTENS)

The Sonopuls 491^a is a combination unit for combining US diathermy and TENS treatment. This unit generates an US wave and electrical stimulation, which are simultaneously transmitted into a patients' skin. US parameters were continuous mode, stroking technique, 1.0 W/cm² of power, 1 MHz of frequency and treatment area of 2× to 3× of the ERA over the anterior aspect of the knee joint. A coupling gel used was a non-drug gel. The TENS setting was adjusted to conventional mode with a frequency of 100 Hz monophasic pulses and 100 μs of pulse duration. The therapist adjusted intensity to a maximally tolerable and non-painful stimulation range from 10 mA to 30 mA. The overall treatment lasted two weeks and consisted of 10 sessions (five sessions per week). Each session lasted 10 min.

Phonophoresis of piroxicam (PhP)

A piroxicam mixed gel^b was used for the PhP treatment. This gel^b was generated using the same process as the previous study.⁽¹⁴⁾ The gel's coloration was similar to the non-drug gel used for the UltraTENS. The US parameters and treatment schedule times were the same as within the UltraTENS group.

Sham TENS

Patients in the PhP group received the sham TENS at a frequency of 100 Hz, pulse duration at 100 μs and intensity less than 4 mA.⁽²⁰⁾ The TENS intensity levels just above subjective sensory threshold have been shown to not relieve pain.^(21,22)

Patients in both groups received paracetamol (500-mg tablet) when unbearable pain was experienced. The number of tablets taken was recorded on the recording card. Additional analgesic drugs such as NSAIDs, opioids or muscle relaxants were not allowed.

Following treatment, the patients were asked to guess which treatment group they had attended. The percentage of correct answers in each group was then used to evaluate the blinding technique's effectiveness.

The most painful or symptomatic knee was chosen when selecting the target knee. However, the right knee was always targeted for treatment if pain or symptom was similar in both knees.

Outcome measures

All patients were interviewed and assessed by an investigator who was blinded to group allocation. Baseline data included age, weight, height, duration of knee pain, side of the knee that was more painful, weight-bearing activity, etc. Outcomes were measured before and after the treatment.

The primary knee pain outcome measure was determined using a 100- mm VAS. The secondary knee functional outcome

was evaluated using the English WOMAC version⁽²³⁾ which includes five joints pain, two joints stiffness and 17 limitations of physical functioning questions. Maximum WOMAC pain for WOMAC pain and WOMAC total scores were 50 and 240, respectively.

An adverse reaction such as skin conditions, gastrointestinal symptoms or hypersensitivity drug reactions was monitored for evaluate treatment safety.

Statistical analysis

SPSS version 17.0^c (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Between- group baseline data comparisons were conducted using the Mann-Whitney and the Chi-square tests for continuous data and categorical data, respectively. The Wilcoxon signed ranks test was used to evaluate within-group pre- to post-treatment knee pain and functional changes. Analysis of covariance (ANCOVA) was used to assess pre- to post-treatment changes in VAS of pain, WOMAC pain and WOMAC total. Baseline age and symptom- duration imbalances were adjusted for. An intention-to-treat approach (last value carried forward) was performed. The statistical significance level was set to $p < 0.05$. A 95% confidence interval was calculated for all comparisons. Sample size was calculated by setting power of 90%, 5% two-tailed significance levels, 20% VAS of effect size and standard deviation of VAS of pain from the previous study⁽¹⁴⁾ This calculation yielded a minimum of 27 patients.

Results

Of the 102 patients that were initially screened, 61 were enrolled (Fig. 1). One patient in the PhP group dropped out due to scheduling conflicts. Thirty-one patients in the UltraTENS, and twenty-nine in the PhP groups, completed their respective treatment programs. Sixty-one patients, 55 women and 6 men, aged 51-80 years old (mean age±SD, 63.4±8.1y) were recruited. Demographic data and baseline characteristics of each group are shown in table 1.

Both groups experienced statistically significant pain and functioning improvements, including VAS of pain, WOMAC pain and WOMAC total ($p < 0.001$) (Table 2). Although improvements were larger in the PhP group in every score, these were not statistically significant (VAS pain; $p = 0.70$, WOMAC pain; $p = 0.43$, WOMAC total; $p = 0.61$) (Table 2).

No patients reported any side effects or adverse reactions from the treatment. Two patients in the UltraTENS and one in the PhP groups reported taking paracetamol to relieve pain experienced within the first few days. There were 48.4 and 37.9 percent of the UltraTENS and the PhP groups, respectively, correctly guessed which group there were in. These difference was not statistically significant ($p = 0.45$).

Discussion

A previous review⁽⁶⁾ has demonstrated that the use of physical agents in symptomatic knee OA is inconclusive. The US and the TENS are commonly used in physical therapy units. However, their efficacy for relieving knee pain remains unconfirmed. Therefore, combining modalities, such as the UltraTENS and the PhP, were developed to enhance pain relief. The PhP has recently been studied⁽¹¹⁻⁴⁾ in a variety of musculoskeletal diseases, including knee OA. The UltraTENS is a

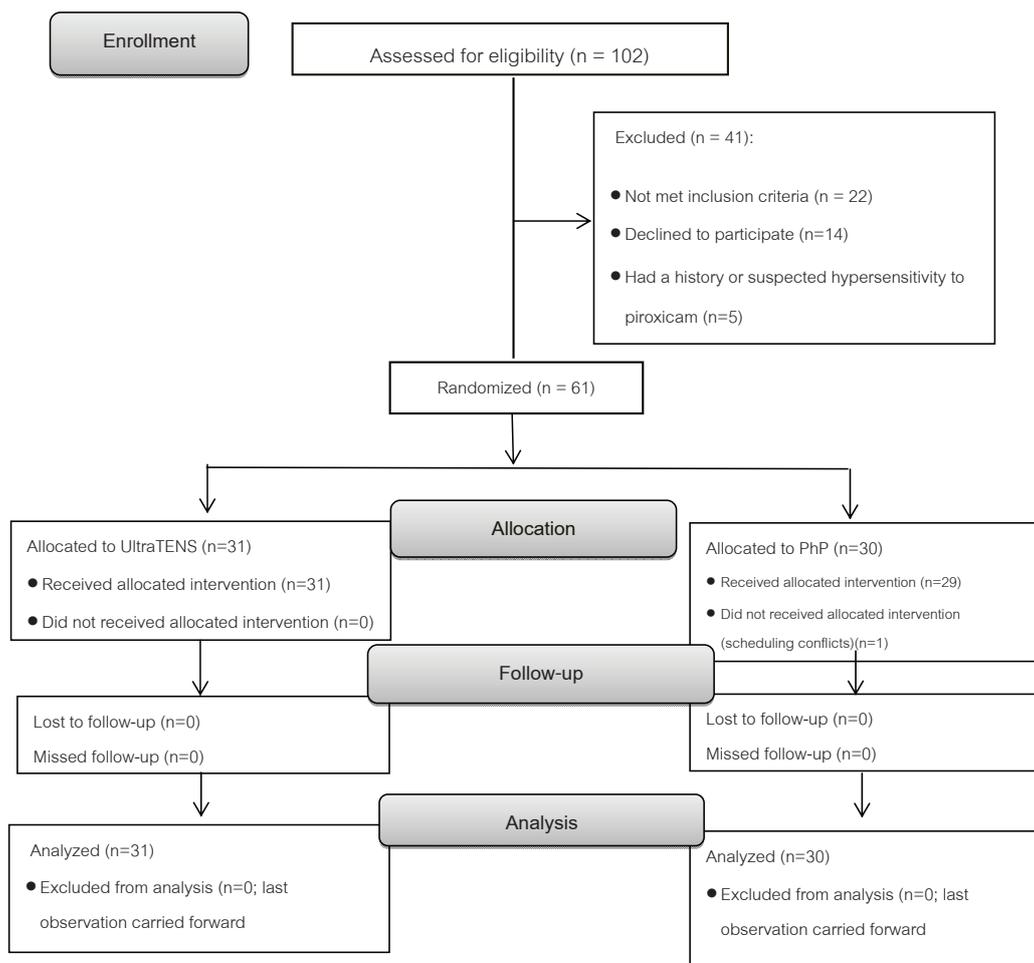


Figure 1. Flow diagram of the study

Table 1. Baseline characteristics of enrolled participants in both groups

Characteristics	PhP (n=30)	UltraTENS (n=31)	p-value
Age (years)	61.4 (6.7)	65.3 (8.9)	0.07 ^a
Women, n (%)	27 (90)	28 (90)	0.65 ^b
BMI (kg/m ²)	24.1 (3.3)	24.4 (3.6)	0.76 ^a
Duration of symptoms (months)	4.4 (5.1)	7.6 (13.3)	0.65 ^a
Weight bearing activity (hours/day)	4.5 (2.3)	4.1 (2.1)	0.43 ^a
Kellgren-Lawrence score, n			
Grade I	3	1	
Grade II	14	17	0.48 ^b
Grade III	13	13	

Mean (SD). BMI, body mass index; PhP, phonophoresis; UltraTENS, ultrasound and TENS

^a, Mann-Whitney test for between groups analysis; ^b, Chi-square test for between groups analysis

common mode in a current version of US machine that could combine with TENS in a single treatment. The UltraTENS has been used in many rehabilitation settings.

Results of the present study demonstrate that the PhP is slightly better than the UltraTENS for relieving pain and improving knee function in mild- to moderate- degrees of symptomatic knee OA. However, these findings are not statistically significant. The PhP may be more practical in general practice because it could conduct by using the old model of ultrasound, and NSAIDs gel is also available and inexpensive.

No serious adverse events occurred in either treatment group. Patients who had a history of piroxicam hypersensitivity or had any contraindication for the US or the TENS were not recruited into the study. For generalizing into a clinical practice, patients who have a drug hypersensitivity should be treated with UltraTENS or vice versa, those who cannot be treated with TENS may switch to PhP.

TENS trial blinding is another complicated issue with conflicting opinions. In most of the TENS literature, a sham TENS has often been administered without electrical currents.⁽²²⁾

Table 2. Mean change from pre- to post-treatment of PhP and UltraTENS groups for VAS, WOMAC pain and WOMAC total scores.

Measures	Treatment groups		Mean of between group difference <i>p</i> -value ^b (95% CI)
	PhP (n=30)	UltraTENS (n=31)	
VAS of pain			
Pre-	67.5 (11.5)	65.4 (10.9)	
Post-	29.0 (20.1)	27.7 (20.4)	
Change	38.5 (20.6)	37.6 (19.9)	0.8 (5.2)
<i>p</i> -value ^a	< 0.001*	< 0.001*	0.70 ^b
95% CI	30.7, 46.1	30.3, 45.0	-9.5, 11.2
WOMAC pain			
Pre-	30.0 (7.0)	30.0 (7.0)	
Post-	15.4 (7.7)	17.3 (9.6)	
Change	15.5 (9.7)	12.7 (8.5)	2.9 (2.3)
<i>p</i> -value ^a	< 0.001*	< 0.001*	0.43 ^b
[95% CI]	11.9, 19.2	9.6, 15.8	-1.8, 7.5
WOMAC total			
Pre-	149.9 (29.6)	141.2 (32.9)	
Post-	73.3 (36.0)	78.1 (45.4)	
Change	76.6 (44.5)	63.1 (36.3)	13.5 (0.4)
<i>p</i> -value ^a	< 0.001*	< 0.001*	0.61 ^b
[95% CI]	60.0, 93.2	49.8, 76.4	-7.2, 34.3

Mean (SD)

^a, Wilcoxon signed ranks test for within-group analysis; * *p*-value is significant.

^b, ANCOVA of change from pre-treatment means (adjusted by age and duration of symptoms); *p*-value is not significant.

A previous randomized, placebo-controlled trial⁽²⁰⁾ reported that sensory threshold stimulation (ranging from 4 to 14 mA) is a good alternative to the commonly used placebo TENS procedure. The former is performed without electrical currents and, therefore, does not produce a perceptible TENS sensation. Authors found that TENS was ineffective for relieving pain when administered at sensory threshold stimulation. In this trial, the PhP group received the sham TENS with the current just above subjective sensory threshold (less than 4 mA) and successful blinding. Less than 50% of participants in each group correctly responded to which group they had been allocated.

Results of the present study support that of the previous trial,⁽¹⁴⁾ demonstrating the PhP to be effective for relieving pain and improving knee function in symptomatic knee OA. The PhP could improve pain symptoms and increase knee function approximately 50% after a 10-session treatment. This study also confirmed that the PhP was compliant and safe. The PhP is a fairly alternative for knee OA treatment, and its potential pain relief benefits warrant further study. Regarding the US frequency of 1 MHz used in both treatments, this frequency correlates with a previous review concluding that US at 1 MHz (2 to 4 cm) could penetrate tissue deeper than at 3 MHz (1 to 2 cm).⁽²⁴⁾

In this study, the UltraTENS used a strong non-painful intensity at high frequency TENS in combination with US. Clinically, TENS is applied at varying frequencies broadly classified as high (>50Hz) or low (<10Hz) TENS. Intensity is determined by patient's response which can be either sensory or motor level TENS. Sensory intensity refers to a strong but comfortable sensation without motor contraction. Higher-frequency stimulation is generally delivered at sensory intensity, and low-

frequency stimulation is delivered at motor intensity. Evidence from animal models suggest that TENS frequencies activate different central anti-nociceptive mechanisms when the current amplitudes are delivered just below motor level threshold.⁽²⁵⁾ A high-frequency TENS activates delta opioid receptors in the brainstem and spinal cord whereas a low-frequency TENS activates mu opioid receptors.⁽²⁶⁾ Another study compared low- (3 Hz) and high- (80 Hz) frequency on blunt pressure pain in healthy human participants and results showed that the latter was superior with a strong, non-painful intensity.⁽²⁷⁾ In addition, there is a study reported that both high-and low-frequency TENS are effective for deep-tissue pain in knee OA.⁽²⁸⁾ The present study showed that the UltraTENS was effective for symptomatic knee OA treatment. However, this method did not significantly differ from the PhP. Determining the potential synergistic effects of the UltraTENS anti-nociceptive mechanism would be interesting to explore in a future.

Another point to be discussed is that the TENS within the UltraTENS has some different procedures from a general TENS i.e., a stimulation time and an applying technique. When applying the UltraTENS, the duration for TENS was just 10-min, due to a maximum US therapy duration. There is currently no consensus regarding to stimulation duration of TENS. In this study, the stimulation time was relatively short. According to a Cochrane review summary, the duration of TENS application in each session ranged from 15 to over 60 min⁽²⁹⁾ whereas another study reported 40 min to be an optimal treatment duration of TENS for reducing pain knee OA.⁽³⁰⁾ Furthermore, the UltraTENS was applied by moving an US probe over an anterior aspect of the knee joint, which covered the patellofemoral and

the tibiofemoral joints. This application differed from the regular TENS procedure. Though there is no general agreement regarding electrode applications, common sites include the medial and lateral aspects of the knee joint, and acupuncture points.⁽²⁹⁾ Applying a moving electrical stimulation over a knee joint might produce different effects from placing a fixed and focused stimulation on a peripheral nerve or concentrated over the painful site only. Further studies are needed in this point.

Ninety percent of subjects in this study were females. Several studies^(31,32) have reported sex differences in knee OA, including: 1) women having higher prevalence and incidence; 2) women having more severe knee OA; and 3) women having significantly worse pain and function impairment. Therefore, a majority of female subjects would limit generalization to the male population. More study is required in this area.

Although our study found that the UltraTENS and the PhP were effective for controlling the knee pain, there were some limitations that should be addressed. First, these results reflect only short-term effects. Therefore, assessment of a longer post-treatment period is needed to identify treatment efficacy for symptomatic knee OA. Second, the use of high-frequency sensory stimulation may have been a limitation, as this technique could not have been applied to low-frequency motor stimulation. Third, the UltraTENS effect is due to the simultaneous US and TENS use. However, effects might have been different if the treatments had been applied separately. Finally, these results could not confidently be applied to male patients.

In conclusion, no significant difference between the PhP and the UltraTENS was found for relieving pain and improving function in Kellgren-Lawrence grades I-III knee OA. Both treatments can be considered effective.

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Suppliers

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- SPSS Inc, 223 S Wacker Dr, 11th Fl, Chicago, IL 60606.

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