

# Comparison of the Efficacy of Different Concentrations of Diclofenac Sodium Phonophoresis (1.16% vs 2.32%) in Patients with Knee Osteoarthritis: a Randomized Double-Blind Controlled Trial

Porovnání účinnosti různých koncentrací sodné soli Diclofenacu (1,16 % vs 2,32 %) při fonoforéze u pacientů s osteoartrózou kolenního kloubu: randomizovaná dvojité zaslepená řízená studie

S. TOLU<sup>1</sup>, M. M. KÖSE<sup>2</sup>, M. C. KORKMAZ<sup>3</sup>, A. ÜŞEN<sup>1</sup>, A. REZVANİ<sup>1</sup>

<sup>1</sup> Istanbul Medipol University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey

<sup>2</sup> Karaman Medical Center, Department of Physical Medicine and Rehabilitation, Karaman, Turkey

<sup>3</sup> Başakşehir Cam and Sakura State Hospital, Department of Physical Medicine and Rehabilitation, Istanbul, Turkey

## ABSTRACT

### PURPOSE OF THE STUDY

The objective of the present study is to compare the efficacy of two different concentrations of diclofenac sodium phonophoresis (DSPH) (1.16% vs 2.32%) in patients with knee osteoarthritis (OA).

### MATERIAL AND METHODS

A randomized, double-blind, controlled design was applied. Ninety patients (mean age  $\pm$  SD, 59.98  $\pm$  8.89 years) who had Kellgren-Lawrence (K-L) grades II to III knee OA were randomly allocated into three groups; 1.16% DSPH, 2.32% DSPH, TUS (30 in each group). Each patient was treated five sessions per week for two weeks. A 100-mm visual analogue scale (VAS) for usual pain and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were evaluated before and after treatment in all groups.

### RESULTS

The VAS pain and WOMAC scores were significantly improved after treatment in all groups ( $p < 0.05$ ). The 2.32% DSPH showed more significant effects than the 1.16% DSPH, both in improving WOMAC- pain and physical function scores ( $p = 0.020$ ,  $p = 0.008$ ) and reducing the VAS pain measure, although it did not reach the level of significance ( $p = 0.077$ ). The 2.32% DSPH was superior to the TUS, both in reducing the VAS pain measure ( $p < 0.001$ ) and in improving WOMAC-pain, stiffness, physical function and total scores ( $p = 0.022$ ,  $p = 0.016$ ,  $p < 0.001$ ,  $p < 0.001$  respectively). 1.16% DSPH significantly reduced stiffness and physical function scores compared with TUS ( $p = 0.042$ ,  $p = 0.047$ ).

### CONCLUSIONS

DSPH and TUS are effective treatments for knee OA. Our results indicated that 2.32% DSPH produces additional benefits to functional improvement and pain reduction compared with 1.16% DSPH in K-L grades II to III knee OA.

**Key words:** diclofenac sodium, knee osteoarthritis, phonophoresis, therapeutic ultrasound, topical formulation.

## INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis with a multifactorial etiology that leads to an eventual loss of joint function and impaired health-related quality of life. The most common symptoms of OA are pain, stiffness and restricted joint mobility. OA can occur in any joint, but knee OA that accounts for approximately 85% of the burden of OA worldwide has been described as the most common form of symptomatic OA. With an increasing number of aged and obese populations, the global prevalence and economic and societal burden of disease are expected to grow steadily in the future (11, 21).

Evidence-based approaches to the treatment of knee OA include non-pharmacologic, pharmacologic, and/or surgical treatment options targeted at relieving pain, facilitating joint mobility to improve function, and modifying risk factors for disease progression (19). According to the recent guideline of the American College of Rheumatology (ACR) on the conservative treatment of knee OA, land-/water-based exercise, mind-body exercises such as Tai Chi and Yoga, lifestyle modification (self-efficacy and management programs, weight loss), braces and cane are strongly recommended non-pharmacological treatment options. Only thermal interventions (locally applied heat

or cold) are conditionally recommended as physical therapy modalities (13). However, therapeutic ultrasound (TUS), a deep-heating agent, has been increasingly used as an effective non-pharmacological option in the treatment of OA, both for pain relief and functional improvement (23). Additionally, TUS waves either pulsed or continuous are widely used as a physical enhancer of absorption of topical pharmacological agents, being called phonophoresis (PH), might emerge as a reasonable therapeutic option in knee OA (8, 23).

Topical anti-inflammatory agents such as steroids, salicylate (piroxicam), NSAIDs (ibuprofen, ketoprofen, diclofenac sodium, etc.) are used with PH (1, 5, 7, 8, 14, 15, 23). In OA, topical administration of NSAIDs offers to provide at least equivalent analgesia, improvement in physical function, and reduction of stiffness compared with oral NSAIDs (18). The most recent guidelines strongly recommend topical NSAIDs for pharmacological treatment of knee OA and consider them before the use of oral NSAIDs due to the safety profile and the least systemic exposure. Therefore PH may emerge as a conservative therapeutic option in the treatment of knee OA. (3, 13). Previous studies evaluated the efficacy of PH with different conditions of exposure to ultrasonic waves (e.g., intensity, frequency, duration, and continuity) and therapeutic form of the topical agent applied (e.g. gel, cream) (1, 5, 7, 8, 14, 15, 23). As the skin permeation may be influenced by drug concentration, formulation composition such as the inclusion of penetration enhancers, and characteristics such as water solubility and acidity, it can be assumed that the effectiveness of PH may also be related to the drug concentration (17). To the best of our knowledge, no studies have assessed the efficacy of PH of different concentrations of topical NSAIDs in the treatment of knee OA. Therefore, in this study, we aimed to compare the clinical efficacy of two different concentrations of diclofenac sodium phonophoresis (DSPH) (1.16% vs 2.32%) in patients with knee OA.

## MATERIAL AND METHODS

### Patients

A total of 98 patients who fulfilled the ACR criteria for the classification of clinical knee OA (2) were consecutively recruited between March 2019 and July 2019. Only patients who were symptomatic during the previous six months and classified by Kellgren and Lawrence (K-L) (12) as grade II-III was included. Exclusion criteria were as follows:

1. presenting positive Lachman, anterior drawer or pivot-shift tests, suggesting knee instability, meniscal tear or positive meniscal tests,
2. a previous history of physical therapy, intra-articular injection or lavage to the same knee in the previous six months,
3. history of traumatic injury, infection or surgery of the lower extremity with knee joint involvement,
4. any type of inflammatory arthritis or other rheumatic diseases,

5. history of malignancy,
6. any contraindications or precautions for the use of TUS (e.g., infection, metal implants, pregnancy, thrombophlebitis, or impaired sensation, skin lesion at the site of application),
7. taking pain relief medications,
8. diclofenac allergy.

### Study design

The present study used a randomized, double-blind, controlled design. The patients were randomly assigned by a computer-generated table of random numbers to one of three study arms. The patients did not know which study group they were in. The study protocol was approved by the Istanbul Medipol University Ethics Committee (10840098-604.01.01-E.3735) and written informed consent was obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Treatment procedures

Ninety patients (19 male, 71 female) with bilateral knee OA, between the ages of 43 and 85 years (mean age  $\pm$  SD, 59.98  $\pm$  8.89) met the eligibility criteria and were randomized into three treatment groups. The more symptomatic or painful knee of each patient was chosen as the index knee. Each group received five sessions per week for 2 weeks (a total of ten sessions) to the index knee. The first group received 1.16 % DSPH, and the second group received 2.32% DSPH. Following the application of 5 cm-long strip of diclofenac sodium (DS) gel to the index knee, continuous ultrasound (Chattanooga Intellect® Mobile Ultrasound-2776) set at a frequency of 1 MHz, and an intensity of 1.5 W/cm<sup>2</sup> was applied on a circular basis for 5 minutes. The third group received TUS with acoustic gel with similar frequency, intensity and duration. The purpose of the TUS group was to serve as the control group. Concomitant local or oral pain relief and anti-inflammatory medications was not allowed. Before starting treatment, the therapist cleaned the patients' skin with an alcohol swab. All treatments were performed with a probe of 5 cm<sup>2</sup> using small, continuous, circular movements over 10 cm<sup>2</sup> skin area on both the medial and lateral part of the knee. Both DS and acoustic gel tubes were purchased by our authors, and all tubes were covered. The patients were blinded to the group allocation. A range of motion, quadriceps strengthening and hamstring stretching exercises were given to all patients in three groups. All patients were instructed about the exercises. The first set of exercises was performed under the supervision of clinical physiotherapists. All patients were instructed to perform 10 repetitions of each exercise as 3 sets a day for two weeks. Blood test (blood count, erythrocyte sedimentation rate, C-reactive protein, liver and kidney function tests) and knee X-ray were taken for each patient at the beginning of the treatment. The outcome measures were assessed immediately after the last treatment by a blinded physician.

## Study assessments

Demographic variables (age, gender, body height and weight), the side of the index knee, symptom duration (months), present medications, history of drug allergies were recorded. Body mass index (BMI) ( $\text{kg}/\text{m}^2$ ) was calculated. Antero-posterior and lateral X-rays of both knees were taken and assessed according to K-L radiological grading system for OA (grade 0 = none, grade 1 = doubtful, grade 2 = minimal, grade 3 = moderate, and grade 4 = severe) (12).

For assessment of treatment efficacy, Visual analogue scale (VAS) for usual pain and the Western Ontario and Mc Master Universities Osteoarthritis Index (WOMAC) scores were recorded before treatment and after the ten sessions finished.

The pain VAS is a unidimensional measure of pain intensity. The scale is most commonly anchored by “no pain” (score of 0) and “pain as bad as it could be” (score of 10 [100-mm scale]) on a horizontal line. Patients were asked to mark the point on that line, corresponding best to the current status of their knee pain. A higher score represents greater pain intensity.

The WOMAC index consists of 24 questions distributed into three subscales: pain (5 questions), stiffness (2 questions), and physical function (17 questions). The subscale scores can vary, with pain ranging from 0 to 20 points; stiffness, 0 to 8 points; and physical function, 0 to 68 points. Higher scores indicate worse pain, stiffness, and functional limitations (4, 20).

## Statistical analysis

Data were analyzed using the IBM SPSS for Windows version 23.0 software (IBM Corp. Armonk, NY, USA). The Shapiro-Wilk test was used to evaluate the normality of data. Descriptive analyses were presented as mean  $\pm$  SD and median (minimum–maximum) for continuous variables. Categorical variables are expressed as counts and percentages. Between-group comparison, we used analysis of variance (ANOVA) and Kruskal-Wallis test for continuous variables, and Pearson chi-square test for categorical variables. Dunn’s post hoc test was used to compute pairwise comparisons. Within-group differences toward the baseline values were evaluated using the Wilcoxon signed-rank test. A *p*-value of 0.05 or less was considered significant.

## RESULTS

A total of 98 patients with knee OA were assessed for eligibility, of whom 90 were enrolled. Two patients were excluded because of a history of knee surgery; four were excluded due to a recent intra-articular steroid injection to the knee, two patients declined to participate. 90 patients were randomly allocated to three study arms; 30 (33.3 %) were treated with 1.16 % DSPH, 30 (33.3 %) were treated with 2.32% DSPH, and 30 (33.3 %) were treated with TUS. All enrolled patients completed the allocated treatment without any dropouts (Fig. 1).

Baseline characteristics of the patients were given in Table 1. There was no statistically significant difference

between the three groups in terms of the demographic characteristics (age, gender and BMI) and the disease-related variables (symptom duration, K-L grades, baseline VAS, and WOMAC scores) ( $p > 0.05$ ).

The within- and between-group changes in VAS pain and WOMAC scores were shown in Table 2. VAS pain significantly decreased from baseline in all treatment groups ( $p < 0.001$ ). Similarly, WOMAC pain, stiffness, physical function and total scores were significantly improved in all groups following the treatment ( $p < 0.05$ ). When changes in VAS and WOMAC scores over time were compared between treatment groups, there were statistically significant differences among the three groups for all study outcomes ( $p < 0.001$ ,  $p = 0.008$ ,  $p = 0.010$ ,  $p < 0.001$ ,  $p < 0.001$ , for VAS pain, WOMAC pain, WOMAC stiffness, WOMAC physical function, and WOMAC total scores, respectively).

Pairwise comparison of the groups was shown in Table 3. Compared with TUS group, %2.32 DSPH group got significantly more improvement in VAS pain, WOMAC pain, stiffness, physical function and total scores ( $p < 0.001$ ,  $p = 0.022$ ,  $p = 0.016$ ,  $p < 0.001$  and  $p < 0.001$  respectively), however, %1.16 DSPH group demonstrated better improvement in only WOMAC stiffness and physical function scores ( $p = 0.042$ ,  $p = 0.047$ ). Subgroup analysis between DSPH groups showed that 2.32% DSPH was significantly more reduced WOMAC-pain, physical function and total scores than %1.16 DSPH ( $p = 0.020$ ,  $p = 0.008$ ,  $p = 0.008$  respectively). No side effects were observed in patients due to treatment.

## DISCUSSION

The aim of the present study is to compare the short term clinical efficacy of two different concentrations of DSPH (1.16% vs. 2.32%) and TUS in patients with knee OA. Two main findings emerged from the analysis of study results:

1. DSPH and TUS are effective and well-tolerated treatments on improving physical function and reducing pain and stiffness in knee OA,
2. 2.32% DSPH produce additional benefits to functional improvement and pain reduction compared with 1.16% DSPH in knee OA.

PH and TUS have been widely used non-invasive, low-risk, pain-free methods in the treatment of musculoskeletal disorders. TUS, a deep heating modality, uses mechanical energy, which is produced by sound waves at different frequencies. Biological responses, including muscle relaxation, induction of tissue regeneration and reduction of inflammation can be induced (9, 23). PH is applied in the same manner as TUS and enhances cutaneous absorption of topical drugs from the skin into the deeper target tissues; therefore, increasing drug effectiveness is expected (9). Although it was reported that PH decreases pain and inflammation in OA, its superiority to TUS is still based on many contradictory studies (5, 14, 15, 23). Kozanoğlu et al. compared the therapeutic efficacy of 5% ibuprofen PH and TUS in the patients

Table 1. Baseline characteristics of the patients with knee osteoarthritis

	2.32% DSPH (n=30)	1.16% DSPH (n=30)	TUS (n=30)	p
Age (year), median (min–max)	59 (43–85)	58 (45–84)	61 (48–68)	0.624
Gender (M/F), n	6/24	7/23	6/24	0.935
BMI (kg/m <sup>2</sup> ) (mean±SD)	31.62±5.29	29.93±4.61	31.31±4.59	0.359
Symptom duration (month), median (min–max)	12 (2–120)	11 (3–121)	12 (1–72)	0.385
Radiological grade, n (%)				0.111
K-L grade 2	12 (40)	17 (56.7)	20 (66.7)	
K-L grade 3	18 (60)	13 (43.3)	10 (33.3)	
VAS for pain, mm	7 (5–10)	7 (5–10)	7 (3–10)	0.671
WOMAC score				
Pain	10 (4–16)	6 (4–15)	8.5 (5–17)	0.058
Stiffness	4 (0–8)	3 (2–6)	4 (0–8)	0.494
Physical function	33 (11–53)	25.50 (14–53)	30.50 (10–58)	0.293
Total	49.50 (16–75)	36.26 (19.20–70)	46.87 (20.83–86.46)	0.152

BMI: body mass index; K-L: Kellgren-Lawrence; DSPH: diclofenac sodium phonophoresis; TUS: therapeutic ultrasound  
VAS: visual analogue scale; WOMAC: Western Ontario and Mc Master Universities Osteoarthritis Index

with knee OA. Significant within-group improvements for pain severity and walking performance were found in both groups without being superior to each other (14). Another study conducted by Boyacı et al. in 101 patients with knee OA compare the efficacy of three different deep heating modalities: ketoprofen PH, short-wave diathermy, and TUS, none of them are found superior to the others (5). In contrast, Luksurapan et al. compared the efficacies of 0.5 % Piroxicam PH and TUS of patients with knee OA, PH was reported to be superior to TUS in reducing pain (15).

There are few studies on the evaluation of the effect of DSPH in musculoskeletal disorders. In one of the randomized controlled studies, Akinbo et al. reported significant improvement in pain, stiffness, physical function, 20-meter walking time and range of motion of knee with %1 DSPH, %15 methyl salicylate cream PH (MSPH) and TUS in knee OA. However, improvement in WOMAC scores, 20-meter walking time and range of motion of the knee joint for DSPH was found to be significantly better than the MSPH almost doubling that of TUS (1). This result explained that DS, which has a higher molecular weight used in gel preparation, provides better permeability for ultrasonic waves than cream-based methyl salicylate. In another study, both continuous and pulsed ultrasound DSPH were found effective for improvement of pain and functional status of patients with knee OA than a topical application of diclofenac gel but no significant difference was detected between each other (8). By contrast, Meshali et al. demonstrated that ultrasound application at 1.5 w/cm<sup>2</sup> continuous mode is optimum for transdermal delivery of ibuprofen across cellulose and rabbit skin membrane (16). Yang et al. showed that the effect of the US duty cycle on the skin permeation was highest with the continuous mode than with the pulsed mode (24). Conse-

quently, previous studies supported that PH enhances the transdermal delivery of a drug as a result of the thermal effects such as an increase in tissue temperature and the mechanical effects such as cavitation and acoustic streaming.

A recently published systematic review and meta-analysis has been demonstrated that TUS is a safe treatment to relieve pain and stiffness and to improve physical function in patients with knee OA via both thermal and non-thermal mechanisms (23). However, as well as the features of the ultrasound technique (frequency and intensity of ultrasound waves, and duration), the physicochemical properties of the topically administered drugs are important factors for the effectiveness of PH. In the present study, PH and TUS were applied five sessions a week, for 2 weeks. By the end of two weeks, our findings revealed significant improvement from baseline for all outcomes in all groups. However, we observed significantly superior improvement in the outcome parameters measured after treatment in the DSPH groups compared with the TUS group. When considered the contradictory results obtained from previous studies, our result may be explained by the drug-related factors which also affect the treatment efficacy of PH.

The ability of the topically administered drug to penetrate the skin and reach the target tissues in sufficient quantity to have a pharmacodynamically active concentration present depend on the composition of the drug formulation such as molecular weight, water solubility and acidity, choice of vehicle (solutions, gels, etc.) and inclusion of penetration enhancers (10). A topical drug with small molecules (<500 g/mol) that are more hydrophilic and also has lipophilic properties pass through stratum corneum more easily. In an in vitro study, gel-based medications were showed higher ability to transmit ultrasound than the cream-based formula-



Table 2. Comparison of the changes within and between patient groups

	2.32% DSPH (n=30)	1.16% DSPH (n=30)	TUS (n=30)	p†
<b>VAS – pain score</b>				
Baseline	7 (5–10)	7 (5–10)	7 (3–10)	<0.001
Post-intervention	3 (0–8)	4 (0–8)	5 (2–8)	
Delta (baseline to post-intervention)	4 (1–7)	3 (–1–7)	3 (0–4)	
<b>p*</b>	<0.001	<0.001	<0.001	
<b>WOMAC – pain score</b>				
Baseline	10 (4–16)	6 (4–15)	8.50 (5–17)	0.008
Post-intervention	4 (0–13)	4 (1–12)	6 (2–14)	
Delta (baseline to post-intervention)	4 (2–7)	2 (0–7)	3 (0–5)	
<b>p*</b>	<0.001	<0.001	<0.001	
<b>WOMAC – stiffness score</b>				
Baseline	4 (0–8)	3 (2–6)	4 (0–8)	0.010
Post-intervention	2 (0–6)	2 (0–4)	2 (0–7)	
Delta (baseline to post-intervention)	2 (0–6)	1 (0–4)	0 (0–2)	
<b>p*</b>	<0.001	<0.001	0.001	
<b>WOMAC – physical function score</b>				
Baseline	33 (11–53)	25.50 (14–53)	30.50 (10–58)	<0.001
Post-intervention	13.50 (3–49)	16.50 (4–49)	25 (5–55)	
Delta (baseline to post-intervention)	11 (4–37)	7.5 (–3–27)	4 (0–19)	
<b>p*</b>	<0.001	<0.001	<0.001	
<b>WOMAC – total score</b>				
Baseline	49.50 (16–75)	36.26 (19.20–70)	46.87 (20.83–86.46)	<0.001
Post-intervention	20 (5–68)	21.12 (5.76–63)	34.38 (10.42–79.17)	
Delta (baseline to post-intervention)	16.81 (6–48.96)	10.50 (–2.88–36.48)	9.38 (0–27.09)	
<b>p*</b>	<0.001	<0.001	<0.001	

VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Index; DSPH: diclofenac sodium phonophoresis; TUS: therapeutic ultrasound  
 Data are presented as median (min–max); p<0.05 was considered statistically significant.  
 p\*: p value for the comparison of within-group differences from baseline to post-intervention, Wilcoxon test  
 p†: p value for between-group comparisons of delta values, Kruskal-Wallis test

tions (6). The diclofenac is available in a variety of topical formulations such as gels and solutions, lotion, lecithin or epolamine gel, patch, or plaster which have a range of doses. Topical diclofenac has a small molecular weight (296 g/mol) with both lipophilic and hydrophilic properties; thus, DS formulated in gel formulation can access all target tissues in OA treatment (25).

The present study hypothesized that the drug concentration of the topical agent is also an important determinant of clinical effectiveness in PH treatment. To confirm this hypothesis, PH of 2.32%, 1.16% diclofenac gel and TUS (serve as the control group) were compared. Pairwise comparisons between PH groups were shown that 2.32% DSPH was significantly more effective than 1.16% DSPH in reducing WOMAC-pain, physical function, and total scores. Compared with TUS, 2.32% DSPH provided significantly better improvement in VAS-pain, WOMAC subscale and total score measures.

However, 1.16% DSPH was only decreased WOMAC-stiffness and physical function scores and showed the same effectiveness with TUS in terms of reducing WOMAC-pain score. The scientific interpretation of this finding most likely is related to the drug composition and active drug concentration of gel preparations. In a randomized controlled study including patients with knee OA, 2% solution twice daily has similar efficacy compared with the diclofenac 1.5% solution four times daily, and potentially greater patient compliance than this and other topical diclofenac formulations (less frequent dosing and ease of application) (22).

In our study, the composition of both diclofenac gel formulations is similar except drug concentration. 1.16% gel contains 11.6 mg of the active substance diclofenac diethyl ammonium, which corresponds to 1 g DS and 2.32% gel contains 2.32 g of the active substance diclofenac diethyl ammonium, which corresponds to 2 g DS. Meshali et al. evaluated the effect of formulation

Table 3. Pairwise comparisons of the changes between treatment groups

	p value		
	2.32% DSPH-1.16% DSPH	2.32% DSPH-TUS	1.16% DSPH-TUS
VAS-pain	0.077	<0.001	0.115
WOMAC score			
Pain	<b>0.020</b>	<b>0.022</b>	1.000
Stiffness	1.000	<b>0.016</b>	<b>0.042</b>
Physical function	<b>0.008</b>	<0.001	<b>0.047</b>
Total	<b>0.008</b>	<0.001	0.307

VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Index; DSPH: diclofenac sodium phonophoresis; TUS: therapeutic ultrasound; values of  $p < 0.05$  was accepted as significant and marked bold

composition and PH on the permeation of ibuprofen through the rabbit skin. PH and increased concentration of the drug in the gel were blamed for increased ibuprofen plasma concentration. The authors suggested that PH and composition of the gel (drug concentration, enhancers, etc.) have a significant effect on the transdermal transmission of a drug (16). Therefore, we thought that the superiority of 2.32% DSPH was due to the drug concentration in target tissues that appears to be sufficient to exert a greater therapeutic effect in OA symptoms.

This study has some limitations. Firstly, this study evaluated only the short-term outcome measures. The long-term effectiveness of different concentration DSPH could be provided. Secondly, DS gel in both concentrations with sham ultrasound might be added to confirm the results.

## CONCLUSIONS

In conclusion, the present study is the first to demonstrate the impact of the drug concentration on the PH efficiency in patients with OA. Our data suggest that topical DS in a gel formulation and higher concentration may be more beneficial for PH treatment to get higher efficacy for OA treatment and we believe that these findings will be a basis for further studies to better estimate the clinical efficacy of topical agents with different drug concentrations in PH for musculoskeletal diseases.

## References

- Akinbo S, Owoeye O, Adesegun S. Comparison of the therapeutic efficacy of diclofenac sodium and methyl salicylate phonophoresis in the management of knee osteoarthritis. *Turk J Rheumatol.* 2011;26:111–119.
- Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M, Howell D, Kaplan D, Koopman W, Longley S III, Mankin H, Mcshane DJ, Medsger T Jr., Meenan R, Mikkelsen W, Mqskowitz R, Murphy W, Rothschild B, Segal M, Sokoloff L, Wolfe F. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum.* 1986;29:1039–1049.
- Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, Kraus VB, Lohmander LS, Abbott JH, Bhandari M, Blanco FJ, Espinosa R, Haugen IK, J Lin J, Mandl LA, Moilanen E, Nakamura N, Snyder-Mackler L, Trojjan T, Underwood M, McAlindon TE. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage.* 2019;27:1578–1589.
- Bellamy N. WOMAC: a 20-year experiential review of a patient-centered self-reported health status questionnaire. *J Rheumatol.* 2002;29:2473–2476.
- Boyaci A, Tutoglu A, Boyaci N, Aridici R, Koca I. Comparison of the efficacy of ketoprofen phonophoresis, ultrasound, and short-wave diathermy in knee osteoarthritis. *Rheumatol Int.* 2013;33:2811–2818.
- Cage SA, Rupp KA, Castel JC, Saliba EN, Hertel J, Saliba SA (2013) Relative acoustic transmission of topical preparations used with therapeutic ultrasound. *Arch Phys Med Rehabil.* 2013;94:2126–2130
- Coskun Benlidayi I, Gokcen N, Basaran S. Comparative short-term effectiveness of ibuprofen gel and cream phonophoresis in patients with knee osteoarthritis. *Rheumatol Int.* 2018;38:1927–1932.
- Deniz S, Topuz O, Atalay NS, Sarsan A, Yildiz N, Findikoglu G, Karaca O, Ardic F. Comparison of the effectiveness of pulsed and continuous diclofenac phonophoresis in treatment of knee osteoarthritis. *J Phys Ther Sci.* 2009;21:331–336.
- Goraj-Szczypiorowska B, Zajac L, Skalska-Izdebska R. Evaluation of factors influencing the quality and efficacy of ultrasound and phonophoresis treatment. *Ortop Traumatol Rehabil.* 2007;9:449–458.
- Hagen M, Baker M. Skin penetration and tissue permeation after topical administration of diclofenac. *Curr Med Res Opin.* 2017;33:1623–1634.
- Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. *Lancet.* 2019;393:1745–1759.
- Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. *Ann Rheum Dis* 1957;16:494–502.
- Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, Callahan L, Copenhaver C, Dodge C, Felson D, Gellar K, Harvey WF, Hawker G, Herzog E, Kwoh CK, Nelson AE, Samuels J, Scanzello C, White D, Wise B, Altman RD, DiRenzo D, Fontanarosa J, Giradi G, Ishimori M, Misra D, Shah AA, Shmagel AK, Thoma LM, Turgunbaev M, Turner AS, Reston J. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. *Arthritis & rheumatology (Hoboken, N.J.)* 2020;72:220–233.
- Kozanoglu E, Basaran S, Guzel R, Guler-Uysal F. Short term efficacy of ibuprofen phonophoresis versus continuous ultrasound therapy in knee osteoarthritis. *Swiss Med Wkly.* 2003;133:333–338.
- Luksurapan W, Boonhong J. Effects of phonophoresis of piroxicam and ultrasound on symptomatic knee osteoarthritis. *Arch Phys Med Rehabil.* 2013;94:250–255.
- Meshali M, Abdel-Aleem H, Sakr F, Nazzal S, El-Malah Y. Effect of gel composition and phonophoresis on the transdermal delivery

- of ibuprofen: in vitro and in vivo evaluation. *Pharm Dev Technol.* 2011;16:93–101.
17. Pradal J, Vallet CM, Frappin G, Bariguián F, Lombardi MS. Importance of the formulation in the skin delivery of topical diclofenac: not all topical diclofenac formulations are the same. *J Pain Res.* 2019;12:1149–1154.
  18. Revel FB, Fayet M, Hagen M. Topical diclofenac, an efficacious treatment for osteoarthritis: a narrative review. *Rheumatol Ther.* 2020;7:217–236.
  19. Schmidt TW. Approach to osteoarthritis management for the primary care provider. *Prim Care.* 2018;45:361–378.
  20. Tüzün EH, Eker L, Aytar A, Daşkapan A, Bayramoğlu M. Acceptability, reliability, validity and responsiveness of the Turkish version of WOMAC osteoarthritis index. *Osteoarthritis and Cartilage.* 2005;13:28–33.
  21. Vina ER, Kwok CK. Epidemiology of osteoarthritis: literature update. *Curr Opin Rheumatol.* 2018;30:160–167.
  22. Wadsworth LT, Kent JD, Holt RJ. Efficacy and safety of diclofenac sodium 2% topical solution for osteoarthritis of the knee: a randomized, double-blind, vehicle-controlled, 4 week study. *Curr Med Res Opin.* 2016;32:241–250.
  23. Wu Y, Zhu S, Lv Z, Kan S, Wu Q, Song W, Ning G, Feng S. Effects of therapeutic ultrasound for knee osteoarthritis: a systematic review and meta-analysis. *Clin Rehabil.* 2019;33:1863–1875.
  24. Yang JH, Kim DK, Yun MY, Kim TY, Shin SC. Transdermal delivery system of triamcinolone acetonide from a gel using phonophoresis. *Arch Pharm Res.* 2006;29:412–417.
  25. Yıldız N, Atalay NS, Gungen GO, Sanal E, Akkaya N, Topuz O. Comparison of ultrasound and ketoprofen phonophoresis in the treatment of carpal tunnel syndrome. *J Back Musculoskeletal Rehabil.* 2011;24:39–47.

**Corresponding author:**

Sena Tolu, MD

Medipol University Faculty of Medicine, Department of  
Physical Medicine and Rehabilitation

TEM Avrupa Otoyolu Göztepe Çıkışı No: 1

34214, Bağcılar/Istanbul, Turkey

E-mail: dr.sena2005@gmail.com