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Detection of Ibuprofen Levels by High Performance Liquid Chromatography After Phonophoresis in the Tissues of Patients with Knee Osteoarthritis: A Controlled Preliminary Study

Diz Osteoartriti Olan Hastaların Dokularında Fonoforez Sonrası Yüksek Performanslı Sıvı Kromatografisi ile İbuprofen Düzeylerinin Saptanması: Kontrollü Bir Ön Çalışma

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ABSTRACT Objective: This study is aimed to detect the drug concentration in articular tissues after phonophoresis application in patients with knee osteoarthritis who were planned to undergo total knee arthroplasty. **Material and Methods:** Seventeen patients with grade 4 knee OA were allocated to 6 groups according to ultrasound parameters and three sessions of ibuprofen phonophoresis were applied before surgery. Six groups were divided into as follows: Group 1; 5 minutes, frequency 0 MHz, power 0 W/cm^2, continuous mode; Group 2; 5 minutes, frequency 1 MHz, power 1 W/cm^2, continuous mode; Group 3; 5 minutes, frequency 1 MHz, power 1.5 W/cm^2, continuous mode; Group 4; 5 minutes, frequency 1 MHz, power 1.5 W/cm^2, pulse mode; Group 5; 8 minutes, frequency 1 MHz, power 1.5 W/cm^2, continuous mode; Group 6; 5 minutes, frequency 1 MHz, power 2 W/cm^2, continuous mode. Bone, synovial fluid and synovial tissue samples were obtained from patients during the surgery. A high-performance liquid chromatographic method was used for the determination of ibuprofen levels from isolated human synovial fluid, synovial tissue and bone. **Results:** Ibuprofen was detected to the articular tissues of patients. The highest concentrations of ibuprofen in synovial fluid were detected in Group 3 and 5. The highest concentrations in bone were obtained in Group 2 and in synovial tissue were obtained in Group 2 and Group 3. **Conclusion:** Optimal penetration of ibuprofen to articular tissues was obtained with 1 MHz and 1-1.5 W/cm^2, and continuous ultrasound mode. Phonophoresis is seemed as an effective treatment modality in patients with OA.

Keywords: Knee osteoarthritis; physical therapy; ibuprofen; phonophoresis

ÖZET Amaç: Bu çalışmada total diz artroplastisi planlanan diz osteoartritli hastalarda fonoforez uygulaması sonrası eklem dokularındaki ilaç konsantrasyonunun saptanması amaçlanmıştır. **Gereç ve Yöntemler:** Evre 4 diz osteoartritli (OA) 17 hasta, ultrason parametrelerine göre 6 gruba ayrıldı ve ameliyat öncesi 3 seans ibuprofen fonoforezi uygulandı. Altı grup aşağıdaki gibi ayrılmıştır: Grup 1; 5 dakika, frekans 0 MHz, güç 0 W/cm^2, sürekli mod; Grup 2; 5 dakika, frekans 1 MHz, güç 1 W/cm^2, sürekli mod; Grup 3; 5 dakika, frekans 1 MHz, güç 1,5 W/cm2, sürekli mod; Grup 4; 5 dakika, frekans 1 MHz, güç 1,5 W/cm^2, darbe modu; Grup 5; 8 dakika, frekans 1 MHz, güç 1,5 W/cm^2, sürekli mod; Grup 6; 5 dakika, frekans 1 MHz, güç 2 W/cm^2, sürekli mod. Ameliyat sırasında hastalardan kemik, eklem sıvısı ve eklem dokusu örnekleri alındı. Yüksek performanslı sıvı kromatografik yöntemi, izole edilmiş insan eklem sıvısı, eklem dokusu ve kemikten ibuprofen seviyelerinin belirlenmesi için kullanıldı. **Bulgular:** Hastaların eklem dokularında ibuprofen tespit edildi. Sinovyal sıvıda en yüksek ibuprofen konsantrasyonları Grup 3 ve 5'te tespit edildi. Kemikte en yüksek konsantrasyonlar Grup 2'de elde edildi ve sinovyal dokuda Grup 2 ve Grup 3'te elde edildi. **Sonuç:** İbuprofenin eklem dokularına optimum penetrasyonu, 1 MHz ve 1-1.5 W/cm^2 ve sürekli ultrason modu ile elde edildi. OA'lı hastalarda fonoforez etkili bir tedavi yöntemi olarak görülmektedir.

Anahtar Kelimeler: Diz osteoartriti; fizik tedavi; ibuprofen; fonoforez

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Phonophoresis is a technique by which therapeutic ultrasound is used to introduce drugs through intact skin into the subcutaneous tissue. It is a noninvasive method which encompasses positive benefits especially having less adverse events than the application of drugs by oral or parenteral forms.[1,2]

It is accepted that the facilitation of drug permeation has been happened by three ways: convection, cavitation and thermal effects.[3] The mechanism of action is based on the penetration of drugs through the micro-cannula in stratum corneum that occurs due to cavitation effects of therapeutic ultrasound. Previous studies have shown that the formation of cavitation increases with frequencies below 1 MHz, whereas the high frequencies prevent this formation.[1,4] The other mechanism of action is the increased temperature of skin which causes the enhanced percutaneous absorption. It is reported that the increased percutaneous absorption has been achieved by using of 1-3 MHz frequency on phonophoresis.[5] Therewithal the various frequencies in the range of 20 kHz-16 MHz has been used by the studies. The exact underlying mechanism of transdermal delivery of drugs by phonophoresis is not clear. Therapeutic ultrasound has two main modes: pulse and continuous. Continuous ultrasound modality has thermal effects whereas pulsed ultrasound provides mechanical effects such as cavitation, acoustic streaming, microstreaming, increased skin pore size, and increased pore numbers and intercellular space.[6] Pulse mode can be more effective for drug penetration due to the cavitation effect but the thermal effect on pore permeability of continuous mode could be more appropriate for phonophoresis.

Although there are many in vitro and animal studies on transdermal delivery of phonophoresis, there are a few clinical studies. In a study, transdermal delivery of the gel form of ibuprofen in rabbit model was investigated. In another study, serum level of dexamethasone in human volunteers after the application of phonophoresis was investigated. Significant level of drugs were obtained in both studies. In general, functional outcomes of phonophoresis were evaluated and conflicting results were reported.[7-13]

There is no clinical study in the literature evaluating the drug levels at target tissues of human after the application of phonophoresis in patients with osteoarthritis (OA). The aim of this study was to evaluate the ibuprofen levels in human knee articular tissues and to determine the optimal therapeutic ultrasound parameters after the application of phonophoresis in patients undergone knee arthroplasthy.

MATERIAL AND METHODS

This controlled, single blind clinical trial was performed at Çukurova University, Faculty of Medicine and Faculty of Science. Ethical approval was obtained from the Çukurova University Faculty of Medicine Non-invasive Clinical Research Ethics Committee with the approval decision number 14-28/5 (date: February 14, 2014). The Declaration of Helsinki protocols were followed, and the patients provided written informed consent.

All of the participants underwent a detailed systemic physical examination. The patients who had been diagnosed with Grade 4 knee OA regarding Kellgren-Lawrence classification and had planned to undergo total knee arthroplasty by orthopedics department were included in the study. The inclusion criteria were; (i) >50 years age, (ii) patients who did not receive ibuprofen for at least 6 months. Exclusion criteria were; (i) allergy to ibuprofen, (ii) major trauma or surgery to target knee, (iii) history of cancer, (iv) an open wound around the knee where phonophoresis was applied. The study was designed as including six groups with three patients in each (there were 2 patients in Group 4) (Figure 1, Table 1, Table 2). Patients were randomly assigned to each group by a computer generated list of random numbers. Six groups were divided into as follows: Group 1; 5 minutes, frequency 0 MHz, power 0 W/cm^2, continuous mode; Group 2; 5 minutes, frequency 1 MHz, power 1 W/cm^2, continuous mode; Group 3; 5 minutes, frequency 1 MHz, power 1.5 W/cm^2, continuous mode; Group 4; 5 minutes, frequency 1 MHz, power 1.5 W/cm^2, pulse mode; Group 5; 8 minutes, frequency 1 MHz, power 1.5 W/cm^2, continuous mode; Group 6; 5 minutes, frequency 1 MHz, power 2 W/cm^2, continuous mode.

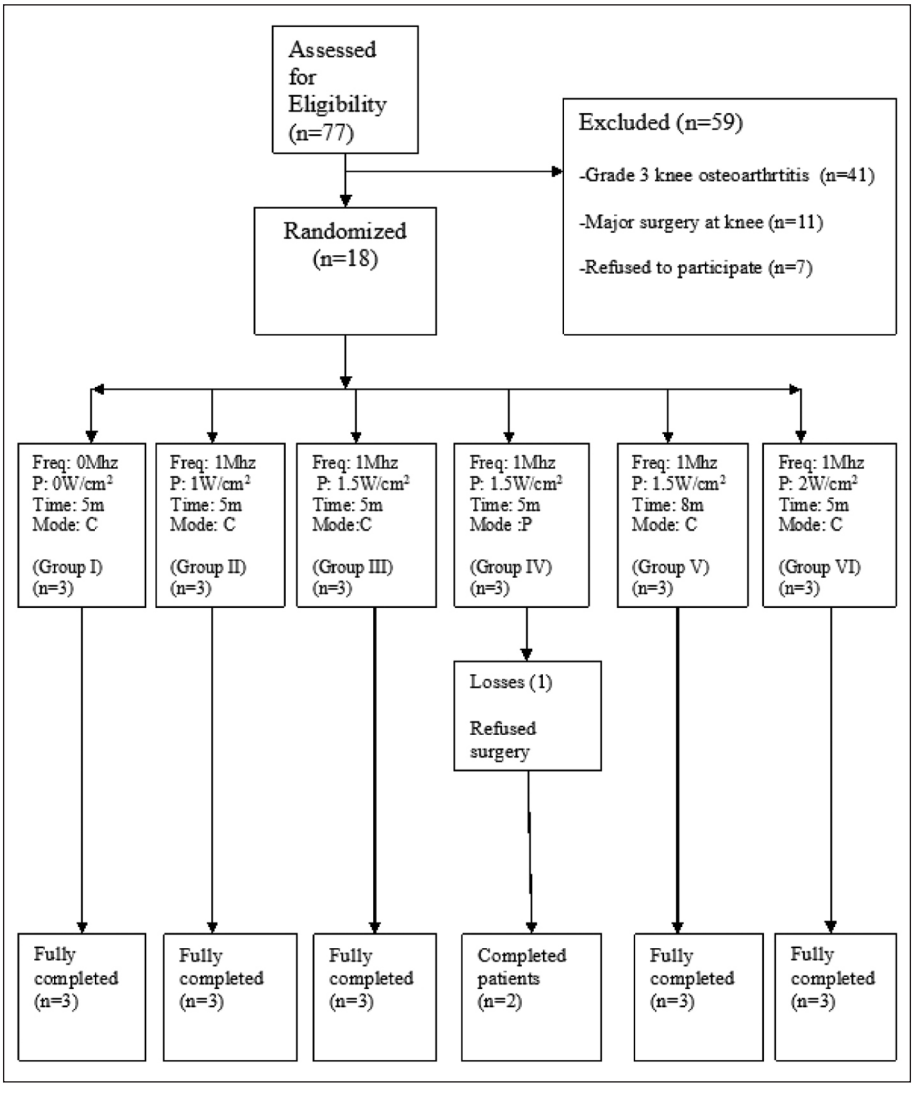

FIGURE 1: Flow charts of the participants. Freq: Frequence; P: Power; M: Minute; C: Continue; P: Pulse.

The penetration of ibuprofen by phonophoresis was evaluated but latest status of complaints of patients before the surgery was not.

Total 17 patients with diagnosis of Grade 4 knee OA were recruited in the study. All patients were female. The group which was applied frequency 0 MHz and power 0 W/cm^2 was considered as sham. Three sessions of ibuprofen phonophoresis were applied on consecutive days for just before the surgical procedure with different periods and parameters of therapeutic ultrasound. Five gram of ibuprofen cream was applied for phonophoresis after stirring with aqua gel. Gel forms of topical agents were more suitable for phonophoresis application but gel form of ibuprofen was not available.

Surgery was performed after 6-8 hours of the last phonophoresis application. Bone, synovial fluid and synovial tissue samples were obtained from patients during the surgery. Bone samples were obtained from tibia and femur, and these samples were homogenized via a grinder. All tissues were maintained at -70°C until the chemical analysis process. All samples were analyzed three times and the average was considered as a result. The orthopedic surgeon and chemist were blind during these procedures.

CHEMICAL ANALYSIS

Acetonitrile [high performance liquid chromatography (HPLC) grade], acetic acid (glacial), ethanol (absolute), diethyl ether (99.7%) were purchased (Merck

TABLE 1: The application parameters of groups.

Group	Time	Frequense (MHz)	Power (W/cm²)	Mode
1 (control)	5 minutes	0 MHz	0	Continue
2	5 minutes	1 MHz	1	Continue
3	5 minutes	1 MHz	1.5	Continue
4	5 minutes	1 MHz	1.5	Pulse
5	8 minutes	1 MHz	1.5	Continue
6	5 minutes	1 MHz	2	Continue

TABLE 2: Demographic data and levels of ibuprofen of patients.

	Patient	Age (Mean±SD)	BMI (Mean)	Synovial fluid (µg/g)	Synovial tissue (µg/g)	Bone (µg/g)
1. Group	1. Patient	59±15.044	30.81	4.74±0.193	0.90±0.042	1.12±0.050
	2. Patient	84±15.044	26.81	0.00*	0.13±0.005	0.22±0.010
	3. Patient	57±15.044	27.54	2.70±0.120	0.05±0.002	0.20±0.010
2. Group	4. Patient	72±5.568	43.87	2.18±0.089	0.21±0.010	7.54±0.356
	5. Patient	68±5.568	39.06	0.97±0.040	3.83±0.178	0.51±0.021
	6. Patient	61±5.568	28.95	1.32±0.062	0.57±0.024	1.71±0.056
3. Group	7. Patient	50±11.790	40.37	0.00 *	0.29±0.013	0.44±0.022
	8. Patient	57±11.790	45.77	***22.95***±1.13	4.63±0.228	4.08±0.200
	9. Patient	73±11.790	39.47	4.54±0.211	1.24±0.056	0.02±0.001
4. Group	10. Patient	72±14.142	25.80	0.80±0.036	0.18±0.007	0.21±0.010
	11. Patient	52±14.142	33.57	1.10±0.051	0.02±0.001	0.12±0.005
5. Group	12. Patient	74±7.506	32.44	***9.10***±0.366	0.19±0.008	0.11±0.005
	13. Patient	66±7.506	35.55	1.60±0.079	0.16±0.007	0.19±0.008
	14. Patient	59±7.506	37.72	4.90±0.219	0.05±0.003	0.17±0.006
6. Group	15. Patient	70±8.185	29.38	***19.90***±0.916	0.27±0.011	0.09±0.003
	16. Patient	65±8.185	40.39	1.10±0.054	0.32±0.016	0.51±0.015
	17. Patient	81±8.185	38.05	0.00*	0.06±0.003	0.14±0.007

*Synovial fluid was not obtain from this patients; BMI: Body mass index; SD: Standard deviation.

Group, Germany), Water (HPLC grade) was obtained from a Millipore System. Agilent solid phase cartridge 6 mL-1,000 mg sampling, Ibuprofen (purity >99%) (Biofarma, Türkiye). For knee, powdered was used TissueLyser II QIAGEN, USA.

Preparation of Standard Solutions: Standard stock solutions of ibuprofen (5 mg mL^{-1}) were prepared separately in the mobile phase. From the standard stock solutions, suitably diluted standard solutions were prepared to contain 0.1, 0.5, 1.0 and 2.0 mg mL^{-1} of ibuprofen.

Extraction of human synovial fluid, knee and synovial tissue: 0.5 g of synovial fluid was weighed and 20 mL of 2% Na_2CO_3 for synovial fluid was directly added for extraction of ibuprofen. 2-8 g of bone was taken and powdered by shaking with TissueLyser II equipment and then 50 mL of 2% Na_2CO_3 was added for extraction of ibuprofen. 10-25 g of synovial tissue was weighed and blended before the extraction. Then 50 mL of 2% Na_2CO_3, was added for extraction of ibuprofen. All the samples were sonicated by ultrasonic bath about 30 min at room temperature and then the mixtures were filtered through no 40 filter paper (Whatman, Merck & Sigma Aldrich, Germany). The alkaline aqueous mixture containing ibuprofen was extracted three times to eliminate or-

ganic matters insoluble in water by using 10 mL of ether for synovial fluid and 20 mL of ether for both synovial tissue and bone alkaline mixture. After pH, was adjusted to 3.5, solid phase extraction was carried out by solid phase extraction (SPE) Bond Elut C18, Agilent, USA). Ibuprofen was eluted from the cartridge with 25 mL of ethanol. Ethyl alcohol with ibuprofen extract was evaporated by water bath and purged by nitrogen gasses (99.9999%). Then 10 mL of mobile phase was added onto residue and sonicated. The mixture was filtered by 0.22 µm membrane filter for HPLC analysis.

Chromatographic Conditions: A HPLC system (Shimadzu, Japan) was used for the analysis. The column used was Kromasil C18, (5 µm, 25 cmx4.6 mm), A mixture of acetonitrile-water (4:6, v/v; pH 3) was used as mobile phase at a flow rate of 1 mL min^{-1}. A Rheodyne 7125 (Sigma Aldrich, German) with a 20 µL loop was used for the injection of samples. Ultraviolet detection was done at 220 nm, with a sensitivity of 0.05 Absorbance Units Full Scale. The mobile phase was filtered through 0.45 µm membrane filter and degassed. The separation was carried out at room temperature, 25±1°C.

Recovery Study: To check the reliability and suitability of the above method, the recovery experiments were performed with 200 µL of standard solution, which contains (1 mg mL^{-1} of ibuprofen). Ibuprofen was once determined by proposed method by recording the chromatogram, the average result of recovery studies after 3 experiment was 77.15% (Table 3).

RESULTS

Out of the 77 patients recruited from the accessible population, 18 met the selection criteria and were randomly allocated to the groups. One patient in Group 4 refused to undergo surgery (Figure 1). A total of 17 female patients diagnosed as Grade 4 knee OA were included in the study. Mean age of the patients was 65.8 years (range 50-84) and mean body mass index (BMI) was 35.03 (range 25.80-45.77). The application parameters of groups are shown in Figure 1.

It could not be obtained synovial fluid from the 2nd patient in Group 1, 7th patient in Group 3 and 17th patient in Group 6 during the surgical procedure (Table 2 and Figure 2).

The highest concentrations of ibuprofen in synovial fluid were obtained at 1st (4.74 µg/g), 8th (22.95 µg/g), 9th (4.54 µg/g), 12th (9.10 µg/g), 14th (4.90 µg/g) and 15th (19.90 µg/g) patients. On group basis, the Groups 3 (5 min, 1 MHz, 1.5 W/cm^2, continuous mode) and 5 (8 min, 1 MHz, 1.5 W/cm^2, continuous mode) stand out (Table 2, Figure 2).

Maximum amounts for bone were obtained at 4th (7.54 µg/g) and 8th (4.08 µg/g) patients. Ibuprofen concentrations of patients in Group 2 (5 min, 1 MHz, 1 W/cm^2, continuous mode) were higher than in other groups. Maximum synovial tissue concentrations were detected in 5th (3.83 µg/g) and 8th (7.54 µg/g) patients (Table 2, Figure 2). Group 3 was more prominent regarding ibuprofen levels at synovial tissue (Figure 2).

DISCUSSION

In the current study, the ibuprofen concentrations at the articular tissues were evaluated after phonophoresis application and it was tried to find optimal thera-

TABLE 3: Results of recovery studies.

Experiment	Recovery %
Ibuprofen-1	68.92
Ibuprofen-2	74.12
Ibuprofen-3	88.41
Average of recovery	*77.15*

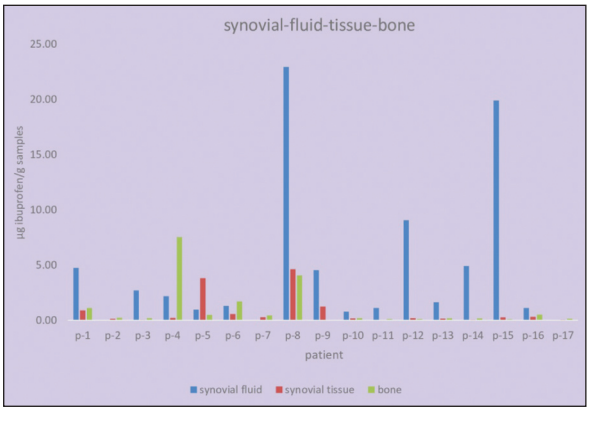

FIGURE 2: The concentrations of ibuprofen in tissues.

peutic ultrasound parameters for phonophoresis. In general, continuous mode, 1 MHz frequency and 1-1.5 W/cm^2 power of therapeutic ultrasound were found as the optimal ultrasound parameters for phonophoresis in these group of patients.

Current guidelines for knee OA include the nonsteroidal anti-inflammatory agents as a therapeutic option, especially in the patients with frequent inflammatory symptoms.[2,14-16] However, the adverse effects of these drugs limit their use in a wide range of patients with knee OA. So, topical nonsteroidal anti-inflammatory drugs provide less systemic adverse events than oral forms. But, there is an important barrier for delivery of topical use of drugs on the skin which was known as stratum corneum. The topical use of drugs by ultrasound, which is known as phonophoresis, could eliminate the barrier of stratum corneum. It was used since decades for treatment of various musculoskeletal conditions.[13,17-21] The mechanism of transdermal enhancement by phonophoresis is not clear. However the acoustic cavitation might play an important role for the penetration of drugs. Collapse of microtubules may lead the skin permeabilisation.[22-24] Non-thermal effects of pulsed ultrasound such as cavitation, microstreaming and micromassage were reported as the responsible mechanisms for drug penetration.[6,25,26] However Kim et al. stated that continuous ultrasound is more suitable for drug penetration because of the necessity of long term application of pulsed ultrasound for drug penetration.[27] In the current study, we found that continuous mode was responsible for drug penetration by phonophoresis. We think that the thermal effect of continuous mode can distribute the drug to the superficial vessel and thermal effect causes transient hyperthermia rather than cavitation.[27]

There are some *in vitro* studies investigating the penetration of topical drugs by using therapeutic ultrasound. Franz diffusion cells were used in these studies. Furthermore there were some animal studies concerning the phonophoresis application and the level of drugs in the tissues.[28-35] To the best of our knowledge, this is the first study which analyzed the penetration of drugs by using phonophoresis at human tissue samples.

Penetration of topical drugs by phonophoresis is highly variable from drug to drug. However, it has been suggested that enhancement in skin permeability using phonophoresis depends on ultrasound parameter used including frequency, intensity, and duration of ultrasound application. Wide range of application time of ultrasound has been reported in the literature. It is suggested that the treatment time over 2 minutes was more effective than shorter duration.[24] We applied 5 minutes ultrasound in fourteen patients and 8 minutes of ultrasound in 3 patients in the current study. No superiority was observed in 5 min application over 8 min application by the means of the drug levels in articular tissues (Table 2, Figure 2).

Interestingly, in our study, we observed some drug penetration in sham group (0 MHz and 0 W/cm^2, continuous mode). Although this situation is surprising as the skin permeability is enhanced by the augmented mechanical stress. This result can occur if therapist applies the ultrasound probe to the skin with strong force.

In a review, it was reported that the transdermal transport enhancement induced by low frequency ultrasound (<100 kHz) has been found to be more significant than high frequency ultrasound. However ultrasound at various frequencies (20 kHz-16 MHz) has been used to enhance skin permeability.[4] In the present study, 1 MHz was used which is a commonly used frequency in clinical setting.

Gel or cream form of topical nonsteroidal anti-inflammatory drugs can be used as coupling agents. However, it was reported both in a study of Benson and McElnay, and in a review that gel preparations conduct ultrasound more efficiently than the cream preparations.[2,36] We used the cream form of ibuprofen and aqua gel together in order to enhance the penetration of ultrasound.

Ibuprofen levels were variable in some subgroups. This may be explained by the 6 to 8 hours delay of surgical procedure after the application of phonophoresis as well as different operation time of patients in some subgroups. Also wide range of BMI and age of the patients' might be affected the results. Additionally, subcutaneous adipose tissue and microvascular structure of patients' could have effected the penetration of ibuprofen.

The level of ibuprofen in synovial tissue and bone was different (Table 2, Figure 2). This condition might be indicated the penetration of ibuprofen continued over time. Generally, the results of Group 3 were better than the results of other groups (Figure 2). 1.5 W/cm^2 and 1 MHz of ultrasound parameters were found most effective for the phonophoresis application.

On the other hand, the half-life of ibuprofen is 1.8-2 hours. 6-8 hours standby time for surgery could be accepted as a relatively long period due to the half-life of ibuprofen. Therapeutic plasma level of ibuprofen is 10-30 µg/mL.[37] It was reported that the synovial fluid levels of ibuprofen was 7.5 µg/mL and 10 µg/mL in a study of Whitlam et al., and Glass and Swannell.[38,39] In both studies, ibuprofen was used in oral form. In our study, we reached this level in 3 patients (two patients with 1.5 W/cm, 1 patient with 2 W/cm). However, it should be kept in mind that the samples were obtained after 6-8 hours after surgery.

The mean recovery of study (after three analyzed) was 77.15%. We think that the real level of ibuprofen in articular tissue was higher than the results we obtained in this study.

There were some limitations of the present study; i) the major limitation of the study was the small sample size. Unfortunately, the most eligible patients did not provide the written informed consent although we said that we will obtain a knee tissue material during surgery. ii) The other limitation was the stage of OA. All patients had Grade 4 OA. Different results might be obtained if the patients had different stages of OA. iii) The surgery was performed 6-8 hours after the application of the last phonophoresis session. This condition might have affected the results of the level of ibuprofen. iv) We could not obtain the plasma samples simultaneously. We could discuss the therapeutic dosage of ibuprofen if we had plasma results. v) Wide BMI and age range of patients' in groups might have affected the results.

CONCLUSION

In conclusion, phonophoresis is one of the effective physical treatment modalities for the management of musculoskeletal disorders. The penetration of the same drug may generally be variable on the viable tissues. This condition can be due to individual characteristics including BMI, age, skin features, and vascular disorders. It seems that the parameters of ultrasound as 1.5 W/cm^2, 1 MHz, 5 min were better than other forms with the use of ibuprofen as active drug. Larger trials are needed to clarify the most effective ultrasound parameters and the factors affecting the penetration of drugs by phonophoresis especially in OA patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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