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Short term efficacy of ibuprofen phonophoresis versus continuous ultrasound therapy in knee osteoarthritis

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Summary

Aim of study: To compare the effectiveness of ibuprofen phonophoresis (PH) with conventional ultrasound (US) therapy in knee osteoarthritis.

Method: Sixty patients with a mean age of 59.8 ± 9.0 years were randomly assigned to PH or US groups. Continuous ultrasonic waves of 1 MHz frequency and 1 watt/cm^2 power were applied for 5 minutes to the target knee joint. Acoustic gel without any active pharmacological agent was applied in the US group, whereas cream containing 5% ibuprofen was applied in the PH group for a total treatment period of 10 sessions. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores, pain on passive and active motion, 20 metres walking time, knee range of motion (ROM), and global assessments of disease activity and treatment efficacy by the investigator and by the patients were evaluated before and after therapy. Primary outcome measure of the study was 30% improvement in total WOMAC scores at the end of the study with respective scores at baseline.

Results: At the end of two weeks, 30% improvement in total WOMAC score was observed in 12 (40%) and 14 (46.6%) of patients in the PH and US groups respectively, indicating no significant difference in improvement rates. Pain scores, knee ROM degrees, 20 metres walking time measurements and all global assessment scores also improved significantly in both groups, yet these variables showed no significant differences between the two groups. When treatment efficacy was assessed as satisfaction rates, investigator satisfaction rates were 96.7% and 90%, while patient satisfaction rates were 93.3% and 83.3% in the PH and US groups respectively, suggesting similar satisfaction rates for both treatment methods.

Conclusions: Both therapeutic modalities were found to be effective and generally well tolerated after 10 therapy sessions. Ibuprofen PH was not superior to conventional ultrasound in patients with knee osteoarthritis.

Key words: phonophoresis; ultrasound; treatment; knee; osteoarthritis

Introduction

Osteoarthritis (OA) is a disease chiefly involving deterioration of articular cartilage reflected clinically in gradual development of pain, stiffness and loss of motion in weight-bearing joints. It is the most common articular rheumatic disease, principally affects the elderly and has variable clinical presentations, often carrying significant morbidity. The therapeutic approach is mainly directed at symptoms and many treatment options, including non-pharmacological and pharmacological measures, are recommended in the management of OA. Although non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in symptomatic treatment of OA, NSAIDs and other drug therapies involve potential hazards including gastrointestinal side effects, particularly in the elderly. Physiotherapy is one of the recommended non-pharmacological management options in patients with OA [1, 2].

Physical agents are devices using physical modalities to produce beneficial therapeutic effects. Heat, cold, pressure, light and even electricity have been used for thousands of years to accelerate healing and decrease pain. Heat therapy is applied to obtain analgesia, decrease muscle spasm, increase collagen extensibility and accelerate metabolic processes. Two forms of heat therapy are available. Superficial agents such as hot packs heat the skin and subcutaneous tissues, while deep heating agents such as therapeutic ultrasound

(US) may produce temperature elevations of 4–5 °C at depths of 8 cm [3].

US has been widely used for more than 40 years in the treatment of musculoskeletal disorders such as tendinitis, tenosynovitis, epicondylitis, bursitis and OA. US converts electrical energy into an acoustic waveform, which is then converted into heat as it passes through tissues of varying resistance [4]. There are two different techniques for administration of US therapy. Continuous US, which is typically responsible for the heat effect, uses an unmodulated continuous-wave US beam with intensities limited to 0.5–2.5 W/cm^2. The second approach emphasises ultrasound's non-thermal properties. In this case the beam is modulated to deliver brief pulses of high intensity US separated by longer pauses of no power [3]. Pulsed US has been recommended for acute pain and inflammation, and continuous US for the treatment of restricted movement [5].

In phonophoresis (PH), in addition to deep heating, US is used to enhance percutaneous absorption of drugs. PH was first used to treat polyarthritis of the hand by driving hydrocortisone ointment into inflamed areas in 1954. Since then it has been used in the treatment of various dermatological and musculoskeletal disorders [6–10]. PH with anti-inflammatory and local anaesthetic agents is used in the management of pain and inflammation in musculoskeletal conditions such as epicondylitis, tendinitis, tenosynovitis, bursitis and OA. The technique is non-invasive, well tolerated and involves minimal risk of hepatic and renal injury [4]. Despite extensive clinical experience, there is controversy regarding the efficacy of PH. Clinical studies of topical anaesthetics, corticosteroids and phenylbutazone have shown beneficial effects [4, 5, 11]. PH with diclofenac gel has been found to be highly effective in painful shoulder syndrome [12], and the use of indomethacin PH has provided significant pain relief in patients with temporomandibular joint pain [13]. In contrast, there are studies which have failed to show the efficacy of PH over US. PH with 0.05% fluocinonide did not augment the benefits of US in various musculoskeletal conditions, and serum levels were not detectable after dexamethasone sodium phosphate PH [14]. Bare et al. [15] investigated the phonophoretic delivery of 10% hydrocortisone in healthy volunteers and failed to find a rise in serum cortisol concentrations, which appears to reflect absence of penetration through the epidermis into the underlying vasculature by PH. It is suggested that studies showing the improved penetration of drugs with PH were performed in animals and the results should not be generalised to studies in humans.

Although physical agents are commonly used in physical medicine and rehabilitation outpatient clinics in Turkey, scientific evidence to support their use is insufficient since randomised controlled trials of rehabilitation are limited [16].

In this prospective randomised controlled trial our aim was to evaluate the short-term effectiveness of ibuprofen PH versus continuous US therapy in patients with knee OA.

Patients and methods

The study was conducted at the outpatient clinic of the Department of Physical Medicine and Rehabilitation, Medical Faculty of Cukurova University, Adana. The local ethics committee approved the study protocol and all patients gave written informed consent.

Patients

The patients enrolled in the study were between 40–80 years of age, fulfilled the American College of Rheumatology (ACR) criteria for OA of the knee [17], had been symptomatic for at least 6 months with the knee the primary source of pain or disability, had not responded adequately to treatment with acetaminophen or non-steroidal anti-inflammatory drugs and had Kellgren-Lawrence [18] scores grade II–IV. All the patients included had a minimum score of 25 on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total scores. Patients were excluded from the study if they had any systemic illness or abnormal laboratory test results, dermatological problems, skin allergy to NSAIDs, local ischaemic problems, atrophic or scarred skin and bleeding dyscrasias, had been on any physiotherapy programme or received intraarticular injections in the preceding year, or had symptoms and signs of acute synovitis.

Patients were assessed by one of the first two authors by history and a detailed physical examination. All patients were initially questioned about age, sex, weight, height, duration of knee pain and the target knee (the more symptomatic or painful knee). In patients in whom both knees were symptomatic the more painful knee – or, when symptoms were similar bilaterally, the right knee – was chosen as the target knee joint. Patients were closely questioned on past and present medication. Laboratory analyses, including complete blood count, erythrocyte sedimentation rate, C-reactive protein (CRP), rheumatoid factor (RF) and routine biochemical tests, were performed to rule out secondary causes of OA and other diseases. All patients had negative RF and CRP values as well as haemoglobin >10 gm/dl, total leucocyte count >4000/mm^3, serum creatinine <1.3 mg/dl, and transaminases <45 units/litre.

Between January 2001 and May 2002, 121 patients fulfilling the ACR knee OA criteria were invited to join the study in our outpatient clinic. Of the 121 patients 61 were excluded (15 refused to participate for miscellaneous reasons, nine were outside the age limits, seven had an actively inflamed knee, six had been on a physiotherapy programme in the preceding year, five had secondary OA, four had severe cardiac problems, four had diabetic polyneuropathy, three had had recent knee surgery, three had venous insufficiency, two had grade I OA, two had dermatological problems, and one was on warfarin therapy). Of the 60 patients who were recruited for the study, 49 (81.6%) were receiving NSAIDs (11 meloxicam, 10 naproxen sodium, 9 celecoxib, 8 diclofenac sodium, and 11 others), 5 (8.3%) were receiving paracetamol and 6 (10%) were not receiving pain medication.

Intervention

Following a 10 days' washout period the patients were invited to the physiotherapy sessions. Concomitant use of NSAIDs or analgesics was not permitted throughout the study. The physiotherapy programme was conducted five times a week for two weeks, excluding weekends, for a total of 10 sessions. During the therapy sessions (while the patients were lying supine), hot packs wrapped in toweling were placed on the target knee for 20 minutes, followed by deep heating with US application. In the US group the skin was coated with an acoustic gel not containing any pharmacologically active substance. In the PH group, a 5cm long strip of cream containing 5% ibuprofen (about 175 mg ibuprofen) was applied from the tube over the target knee. US was then applied to the superomedial and lateral parts of the knee by the same therapist stroking the applicator in circular movements. The transducer head was applied to the therapy region at right angles to ensure maximum absorption of the ultrasound energy. Continuous ultrasonic waves with 1 MHz frequency and 1 watt/cm^2 power were applied with a 4 cm diameter applicator (Peterson® 250 Ultrasound equipment Petaş-Turkey). US therapy lasted 5 minutes in each session. To avoid the immediate effects of heat application, the outcome data evaluation was performed two days after completion of the last session.

Study end points

The primary outcome measure of the study was 30% improvement in total WOMAC scores at the end of the therapy programme compared with baseline scores. The WOMAC questionnaire was used to measure pain, stiffness and physical function [19, 20]. WOMAC scores were recorded on a Likert scale of 0–4, where 0 = no pain/limitation; 1 = mild pain/limitation; 2 = moderate pain/limitation; 3 = severe pain/limitation; and 4 = very severe pain/limitation. Maximum scores for stiffness, pain and physical function were 8, 20 and 68 respectively with a total score of 96. The secondary end points were: pain with passive and active motion of the knee joint assessed by visual analogue scale (VAS; 0 = no pain, 100 = most severe pain), the time required to walk a distance of 20 metres "as fast as possible" was measured with a stop-watch and reported in seconds, the range (flexion minus extension) of motion (ROM) of the target knee was measured with a long-arm goniometer. Global assessments of disease activity by investigator (GAD-I) and by patients (GAD-P) were evaluated. GAD-I was performed by the investigator to form a subjective judgment of the disease activity based on the patient's symptoms, functional capacity, physical examination and laboratory parameters using a Likert scale (0 = very poor, 1 = poor, 2 = moderate, 3 = good, 4 = excellent). Patients themselves also used a Likert scale to make a global assessment of their condition (GAD-P). Global assessments of treatment efficacy by investigator (GAE-I) and by patient (GAE-P) were also evaluated with the same Likert scale at the end of therapy.

Statistical analysis

To provide an 80% power of detecting a 30% improvement in WOMAC total scores at a significance level of 5%, a minimum of 30 patients would be required in each group. Thus, in this study, 60 patients were consequently randomised into PH or US groups consisting of 30 patients in each arm.

SPSS 9.0 for Windows package program was used for statistical analysis. All demographic and quantitative data are expressed as mean ± standard deviation. Independent samples t test was used to compare the quantitative values of both groups. Paired samples t test was used to compare the pre- and post-treatment changes in each group. Chi-square test and Mann Whitney-U tests were used to compare qualitative values between the two groups. Changes in the GAD-P and GAD-I scores with treatment were analysed with Wilcoxon signed rank test. P values <0.05 were considered significant.

Results

Patient characteristics

The study population consisted of 60 patients (9 males, 51 females) with a mean age of 59.8 ± 9.0. Baseline characteristics of the patients are given in table 1. There were no significant differences with respect to age, gender, body mass index (BMI), X-ray scores, pain with passive and active motion (VAS), 20 metres walking time, ROM degrees and WOMAC scores. In addition, there were no statistically significant differences in baseline GAD-I and GAD-P scores between the two groups (p >0.05).

All of the enrolled patients completed the study and none were excluded from analysis.

Clinical changes between treatment groups

At the end of two weeks a 30% improvement in total WOMAC score was observed in 12 (40%) and 14 (46.6%) patients in the PH and US groups respectively. No significant difference in the 30% improvement rate was detected between the two groups (p >0.05).

All secondary outcome measures of the current study, including WOMAC scores, 20 metres walking time, ROM degrees, pain with passive and active motion, improved significantly after treatment in both groups. GAD-I and GAD-P also improved significantly within both groups at the end of the study. No statistically significant differences were observed regarding changes in secondary outcome measures between the PH and US groups (table 2). GAE-I and GAE-P are shown in Figure 1. At the end of the study, 2 patients in the PH group rated the treatment efficacy as very poor or poor and 28 patients rated it moderate to excellent, while in the US group 1 patient rated it poor and 25 patients rated it moderate to good. In addition, investigators' ratings of treatment efficacy were poor in 1 patient, moderate in 13 patients and good in 16 patients of the PH group. The respective patient numbers in the US group were 3, 7 and 20.

To assess satisfaction with the treatment, GAE-I and GAE-P scores were classified as dissatisfied or satisfied. Ratings of very poor or poor (0, 1 points) were considered to denote dissatisfaction while moderate, good, excellent (2, 3, 4 points)

Table 1

Baseline characteristics of patients with osteoarthritis of the knee assigned to receive ibuprofen phonophoresis or continuous ultrasound.

		Ibuprofen PH (n = 30)	Continuous US (n = 30)
Age (yr)		60.3 ± 9.2 (41–80)	59.4 ± 8.9 (44–78)
Male/female		5/25	4/26
BMI (kg/m^2)		30.6 ± 4.5 (22.7–41.8)	31.1 ± 5.2 (22.3–43.7)
Duration of pain (yr)		6.4 ± 6.2 (1–25)	4.9 ± 3.9 (1–15)
Kellgren-Lawrence (grade)	II	13	8
	III	13	18
	IV	4	4
Pain with passive motion (VAS) (mm)		47.0 ± 17.0	42.6 ± 20.1
Pain with active motion (VAS) (mm)		41.3 ± 16.0	41.3 ± 16.9
20 metres walking time (seconds)		21.8 ± 6.6	21.0 ± 9.5
Range of motion, degrees		125.0 ± 15.6	124.4 ± 14.5
WOMAC scores			
Pain		9.8 ± 2.7	9.8 ± 2.7
Stiffness		2.8 ± 1.6	3.1 ± 1.6
Physical function		32.3 ± 9.5	32.1 ± 11.6
Total		44.9 ± 12.3	45.1 ± 14.5

Values are mean ± SD (minimum – maximum). OA = osteoarthritis; BMI = body mass index;
WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index (Likert version)
VAS = Visual analogue scale (0 = no pain, 100 = most severe pain)

Table 2

Changes in clinical outcome measures after therapy.

Outcome measure	Ibuprofen PH (n = 30)	Continuous US (n = 30)	p***
	Primary		
WOMAC scores			
Pain	–2.7 ± 2.3**	–3.3 ± 2.7*	0.359
Stiffness	–0.8 ± 1.6*	–1.3 ± 1.4**	0.199
Physical function	–6.9 ± 7.2**	–9.2 ± 7.3**	0.217
Total	–10.4 ± 9.6**	–13.8 ± 10.2**	0.192
	Secondary		
20 metres walking time (seconds)	–3.0 ± 3.1**	–1.9 ± 2.0**	0.102
Range of motion, degrees	4.5 ± 8.3*	3.5 ± 4.8**	0.597
Pain with passive motion, VAS	–16.5 ± 17.5*	–14.9 ± 17.1**	0.727
Pain with active motion, VAS	–15.6 ± 15.3*	–15.0 ± 15.9**	0.882
GAD-P	1.1 ± 0.7*	1.0 ± 0.6**	0.538
GAD-I	1.0 ± 0.5**	0.9 ± 0.5**	0.445

Values are mean ± SD. Negative values signify improvements for all measures except range of motion.
WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index (Likert version).
GAD-P = Global assessment of disease activity by patients. GAD-I = Global assessment of disease activity by investigator.
VAS = Visual analogue scale (0 = no pain, 100 = most severe pain)
P values were determined by 2-sample t test; * p <0.05, ** p <0.001 versus baseline within the treatment group; *** difference between the two treatment groups.

were considered to denote satisfaction with the treatment. Investigator satisfaction rates were 96.7% (n = 29) and 90% (n = 27) while patient satisfaction rates were 93.3% (n = 28) and 83.3% (n = 25) in the PH and US groups respectively (p >0.05). The PH and US groups were similar with respect to satisfaction rates.

No local or systemic side effects were observed in the study population during the treatment.

Discussion

In this randomised controlled study, marked improvements in clinical parameters were obtained with ibuprofen PH or therapeutic US in patients with knee OA, and neither modality was found to be superior to the other.

Therapeutic US is frequently used in physio-

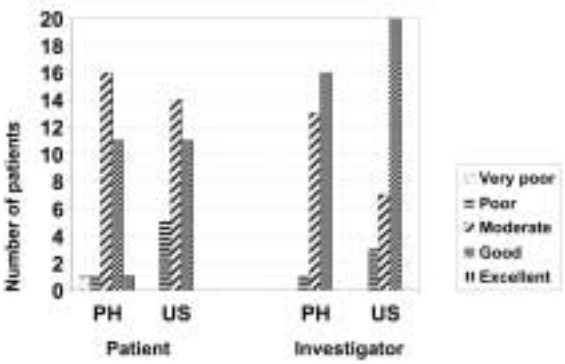

Figure 1
Global assessments of treatment efficacy by patients and investigator.

therapy clinics to treat various musculoskeletal disorders [21, 22]. Although the exact mechanism of action is unknown, heating is the most important effect. It encourages regional blood flow and increases connective tissue extensibility. Non-thermal effects are less understood and include molecular vibration, which increases cell membrane permeability and thereby enhances metabolic product transport [3].

When US is used with specific medication to encourage transdermal penetration of the compound, it is referred to as PH. Significant amounts of drug are picked up by the subcutaneous circulation with PH. Claims of penetration to depths of several centimeters have been made. Use of PH in the practice of physiotherapy may represent up to 30% of the physiotherapy visits in some sites [23]. Approximately 75% of the studies reviewed by Byl [23] indicated some level of effectiveness of US as an enhancer of topically applied drugs.

Ibuprofen cream is one of the widely used agents and exhibits detectable tissue concentrations in deep tissue compartments – more than enough to inhibit inflammatory enzymes even after topical application. It has been reported that high concentrations of the active ingredient can be assessed in the synovial fluid within 14 hours of the last application of ibuprofen cream [24–26]. In a study performed by Dominkus et al. [27] the topical ibuprofen and oral tablet form of the same drug were compared in patients with OA. Drug levels were determined in different tissues at the time of arthroplasty, and higher levels of ibuprofen were found in the plasma, synovial fluid and fascia after oral administration whereas higher levels were observed in muscle and subcutaneous tissue after topical administration.

In this study we proposed that penetration of ibuprofen to the deeper sites is enhanced by PH, resulting in benefits additional to those of conventional therapeutic US. However, the two treatment modalities were found to be equally effective. In a study by Klaiman et al. [4], the efficacy of 0.05% fluocinonide PH versus US therapy was investigated in the treatment of 49 subjects with soft tissue injuries, and the authors found no difference in pain level and pressure tolerance between groups. Smith et al. [28] compared ice massage, ultrasound alone, and iontophoresis and PH with dexamethasone and lidocaine. Although all of these therapies were more effective than the control treatment, none of them was found to be superior to any other. In a double-blind, placebo controlled study; indomethacin PH was used in the treatment of temporomandibular joint pain in 20 patients, and significant pain relief was reported [13]. Similarly, Ciccone et al. [10] evaluated the efficacy of trolamine salicylate PH and ultrasound therapy on delayed onset muscle soreness. The investigators found that ultrasound enhanced the development of delayed onset muscle soreness but this effect was prevented by the application of salicylate PH.

There are limited numbers of randomised controlled trials with PH or therapeutic US treatment in knee OA. Falconer and colleagues reported a randomised controlled trial of the effectiveness of US in relieving stiffness and pain in OA of the knee with chronic contracture. Exercise treatments were preceded by either US or sham US. Both groups showed significant improvement in ROM and pain, with no detected differences between groups. The researchers suggest that US may not contribute to the management of patients with chronic knee stiffness and OA [29]. Their findings are contradictory to ours since our patients showed significant increases in ROM. A possible explanation for this is that none of our patients had a major long-standing contracture.

Welch et al. [30], having searched the literature and found only 3 randomised controlled trials of US therapy in knee OA, concluded that US therapy bestowed no greater benefit than placebo, shortwave diathermy or galvanic current in knee OA. Similarly, in a recent review of therapeutic US Robertson and Baker [22] examined 35 randomised controlled trials published between 1975 and 1999 and only 10 were judged to have acceptable methods. Overall, the reviewers reported finding little evidence that active therapeutic US was more effective than placebo US in treating people with pain or a range of musculoskeletal injuries or in promoting soft tissue healing.

To our knowledge, this is the first study to compare ibuprofen PH with therapeutic US in patients with knee OA. Our primary end point was the functional impact of treatment based on a validated instrument such as WOMAC. Significant improvements in pain with motion, walking time, knee ROM, WOMAC scores, global assessments of disease activity and treatment efficacy by the patients and the investigator were attained in both the PH and US groups in the current study. The degree of improvement was similar in the two groups and PH with ibuprofen did not provide any benefit additional to that from ultrasound therapy. Conventional therapeutic US application was effective in relieving the symptoms in patients with knee OA.

It is possible that the application of hot packs before active therapy may have influenced our results. We set up our protocol in this manner to increase the effect of PH. It is known that pre-

heating the skin enhances transdermal drug delivery [4]. In his extensive review of PH, Byl [23] also suggests that the skin should be pretreated with US, heating, moistening or shaving in order to maximize clinical effectiveness. To avoid the influence of superficial heat on our results, outcome data were collected two days after the completion of therapy sessions.

There are two potential limitations to this study: first, the results reflect the short-term effects of PH or US therapy. Long-term effectiveness is not evaluated. Second, another group receiving sham US would allow us to comment on additional effects of US alone.

For a more definitive answer on the use of PH and therapeutic US in knee OA, large randomised controlled trials are needed.

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References

1 Hough AJ. Pathology of Osteoarthritis. In: Koopman WJ, ed. Arthritis and Allied Conditions. 13th ed. Baltimore: Williams & Wilkins; 1945–1968, 1997.
2 Recommendations for the medical management of osteoarthritis of the hip and knee. American College of Rheumatology subcommittee on osteoarthritis guidelines. 2000 update. Arthritis Rheum 2000;43:1905–15.
3 Basford JR. Physical Agents. In: DeLisa JA, Gans BM, eds. Rehabilitation Medicine: Principles and Practice. Philadelphia: Lippincott-Raven; 483–503, 1998.
4 Klaiman MD, Shrader JA, Danoff JV, Hicks JE, Pesce WJ, Ferland J. Phonophoresis versus ultrasound in the treatment of common musculoskeletal conditions. Med Sci Sports Exerc 1998;30:1349–55.
5 Sharma L. Nonpharmacologic management of osteoarthritis. Curr Opin Rheumatol 2002;14:603–7.
6 Kassan DG, Lynch AM, Stiller MJ. Physical enhancement of dermatologic drug delivery: Iontophoresis and phonophoresis. J Am Acad Dermatol 1996;34:657–66.
7 Tyle P, Agrawala P. Drug delivery by phonophoresis. Pharm Res 1989;6:355–61.
8 Newman JT, Nellermoe MD, Carinett JL. Hydrocortisone phonophoresis. J Am Podiatr Med Assoc 1992;82:432–5.
9 Kamenskaia NS, Fedorova NE. The therapeutic use of iodide-bromide-sodium chloride baths combined with hydrocortisone phonophoresis in patients with osteoarthrosis and gout. Vopr Kurorto Fizioter Lech Fiz Kult 1990;6:47–50 (abstr).
10 Ciccone CD, Leggin BG, Callamaro JJ. Effects of ultrasound and trolamine salicylate phonophoresis on delayed-onset muscle soreness. Phys Ther 1991;71:666–75; discussion 675–8.
11 Van der Windt DA, van der Heijden GJ, van den Berg SG, ter Riet G, de Winter AF, Bouter LM. Ultrasound therapy for musculoskeletal disorders: a systematic review. Pain 1999;81: 257–71.
12 Vlak T. Comparative study of the efficacy of ultrasound and sonophoresis in the treatment of painful shoulder syndrome [abstract]. Reumatizam 1999;46:5–11.
13 Shin SM, Choi JK. Effect of indomethacin phonophoresis on the relief of temporomandibular joint pain. Cranio 1997;15: 345–8.
14 Darrow H, Schulthies S, Draper D, Ricard M, Measom GJ. Serum dexamethasone levels after decadron phonophoresis. J Athl Train 1999;34:338–41.
15 Bare AC, McAnaw MB, Pritchard AE, Struebing JG, Smutok MA. Phonophoretic delivery of 10% hydrocortisone through the epidermis of humans as determined by serum cortisol concentrations. Phys Ther 1996;76:738–45.
16 Philadelphia panel evidence-based clinical practice guidelines on selected rehabilitation interventions for knee pain. Phys Ther 2001;81:1675–700.
17 Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. 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: 1039–49.
18 Ravaud P, Auleley GR, Amor B, Dougados M. Radiographic assessment of progression in knee osteoarthritis. Rheumatology in Europe 1995;24(Suppl 2):129–31.
19 McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): A Review of Its Utility and Measurement Properties. Arthritis Care Res 2001;45:453–61.
20 Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
21 Roebroeck ME, Dekker J, Oostendorp RAB. The use of therapeutic ultrasound by physical therapists in Dutch primary health care. Phys Ther 1998;78:470–9.
22 Robertson VJ, Baker KG. A review of therapeutic ultrasound: effectiveness studies. Phys Ther 2001;81:1339–50.
23 Byl NN. The use of ultrasound as an enhancer for transcutaneous drug delivery: phonophoresis. Phys Ther 1995;75:89: 539–53.
24 Dickson DJ. A double-blind evaluation of topical piroxicam gel with oral ibuprofen in osteoarthritis of the knee. Curr Ther Res 1991;49:199–207.
25 Moore RA, Tramèr MR, Carroll D, Wiffen PJ, McQuay HJ. Quantitive systematic review of topically applied non-steroidal anti-inflammatory drugs. BMJ 1998;316:333–8.
26 Chlud K, Berner G, Wagener HH. Ibuprofen concentrations in subcutaneous fatty tissue, joint capsule and synovial fluid after percutaneous application. Therapiewoche 1985;35:2872–6.
27 Dominkus M, Nicolakis M, Kotz R, Wilkinson FE, Kaiser RR, Chlud K. Comparison of tissue and plasma levels of ibuprofen after oral and topical administration [abstract]. Arzneimittelforschung 1996;46:1138–43.
28 Smith W, Winn F, Parette. Comparative study using four modalities in shin splints treatments. J Orthop Sports Phys Ther 1986;8:77–80.
29 Falconer J, Hayes KW, Chang RW. Effect of ultrasound on mobility in osteoarthritis of the knee. A randomized clinical trial. Arthritis Care Res 1992;5:29–35.
30 Welch V, Brosseau L, Peterson J, Shea B, Tugwell P, Wells G. Therapeutic ultrasound for osteoarthritis of the knee. Cochrane Database Syst Rev 2001;(3):CD003132.

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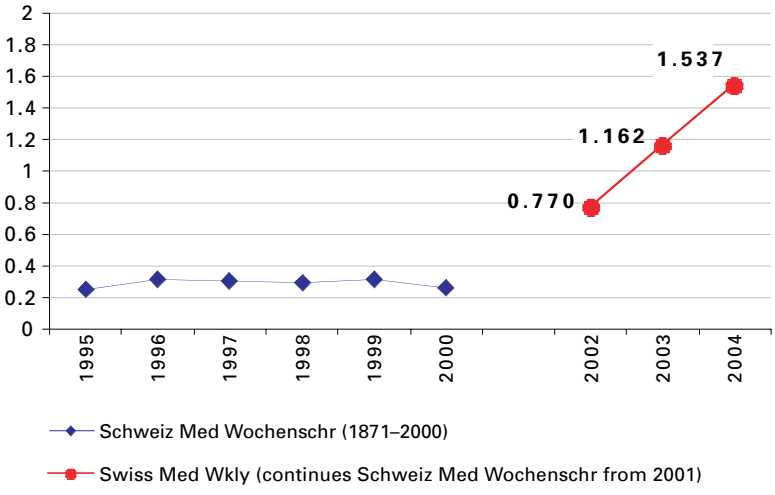

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