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Does Phonophoresis Using NSAIDs Reduce Osteoarthritis Knee Pain?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not phonophoresis using NSAIDs reduces osteoarthritis knee pain.

Study Design: Systematic review of three double-blind randomized controlled trials published between the years 2013 and 2018.

Data Sources: Published peer-reviewed articles obtained through PubMed and Cochrane Collaboration. Articles were selected based on relevance to my clinical question and if they included patient-oriented outcomes.

Outcomes Measured: Pain severity was self-reported by patients using a visual analog scale (VAS) on a continuum of 0-100; 0 representing no pain at all and 100 representing the worst pain imaginable. Participants in all three studies reported pain scores at baseline and after completing 2 weeks of treatment.

Results: The study conducted by Luksurapan et al. showed a mean change from baseline of 67%, a mean of between group difference of 14.73 +/- 5.78, and a P-value of 0.009.[1] The study conducted by Monisha et al. showed a mean change from baseline of 70% and a P-value < 0.00.[2] The study conducted by Oktayoglu et al. showed a mean change from baseline of 23 and a P-value of < 0.05.[3]

Conclusion: All three studies in this EBM review demonstrated reduction of mild to moderate osteoarthritis knee pain with the use of phonophoresis using NSAIDs. Additional research may be indicated to further evaluate treatment outcomes with larger and more diverse patient populations, as well as long-term effects of treatment.

Key Words: Phonophoresis, Osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) is a chronic and progressive degenerative disease in which joint spaces are disrupted due to osteophytic lesions, subchondral sclerosis and cartilaginous erosions.[2,3] Osteoarthritis is the most common cause of disability in adults and can lead to impairment in mobility, pain, and decreased quality of life.[3,4] Hip and knee OA cause the greatest burden in terms of pain, stiffness, and functional disability, which may cause limitations in activities of daily living and the need for prosthetic joint replacements.[2,4]

Osteoarthritis is the most common joint disorder in the US and affects over 30 million adults; up to 13.5% of men and 18.7% of women.[4] Etiology of OA may be multifactorial and some causes may include injuries, overuse of joints, increasing age, poor diet, obesity, genetics, female gender, congenital or developmental abnormalities, joint misalignment or muscle weakness.[5] The incidence of OA is increasing, likely due to the aging population and the increased prevalence of obesity.[4] OA accounts for approximately 11,127 office visits annually in the US.[7] In 2012, osteoarthritis accounted for the highest cause of work loss, affecting more than 20 million people in the work force and costing the US economy over $100 billion annually.[4] In 2013, knee osteoarthritis alone was estimated to contribute to over $27 billion in health care expenditures annually.[4]

The goal of treatment for knee OA is focused on pain relief, improving joint function, and modifying controllable risk factors.[6] There are currently no disease modifying drugs available to treat OA, but there are multiple symptomatic treatment options available for improvement of pain and function.[6] Nonpharmacologic treatment options include physical therapy, exercise, weight loss, walking aids and braces to alter joint loading.[6] Pharmacological treatment options include topical non-steroidal anti-inflammatory drugs (NSAIDs), topical

Capsaicin cream, Acetaminophen, oral NSAIDs, oral Cyclooxygenase-2 (COX-2) inhibitors, intraarticular corticosteroids, and hyaluronic acid injections.[6] Other treatment options include acupuncture, transcutaneous electrical nerve stimulator (TENS), ultrasound, iontophoresis, and surgery; total joint replacement and arthroscopic debridement.[6] Using a combination of therapeutic approaches is preferred as drug options typically have more potential risk for adverse effects.[6]

Phonophoresis using NSAIDs may be used as an alternative treatment option for the reduction of osteoarthritis knee pain. Phonophoresis uses ultrasound to enhance percutaneous absorption of drugs.[1] Ultrasound is a deep heating agent that can reduce pain by inducing tissue regeneration, reducing inflammation, and relaxing muscle tissue.[1] Phonophoresis can use these therapeutic factors with the addition of NSAIDs, such as piroxicam or diclofenac dimethylamonium gel, to enhance reduction of pain and inflammation.[1] This therapeutic method has the advantage of providing local treatment without the renal, cardiac, and gastrointestinal side effects of oral medications.[3] Administration of topical NSAID agents can be used to maintain stable plasma levels while also maintaining a good safety profile.[8] This paper evaluates three double-blind randomized controlled trials comparing the efficacy of phonophoresis using NSAIDs in the reduction of osteoarthritis knee pain.

OBJECTIVE

The objective of this selective evidence-based medicine (EBM) review is to determine whether or not phonophoresis using NSAIDs reduces osteoarthritis knee pain.

METHODS

The articles selected for this systematic review include three double-blind randomized controlled trials. The population consists of patients with osteoarthritis knee pain. The treatment

group receiving phonophoresis using NSAID gel was compared to the experimental group receiving ultrasound with nonpharmacologic gel. Outcomes were measured using a visual analog scale (VAS) to assess the efficacy of phonophoresis with NSAIDs on the reduction of osteoarthritis knee pain.

"Phonophoresis" and "osteoarthritis" were the keywords used to find appropriate articles for this review through PubMed and Cochrane databases. All articles obtained were written in English and were published in peer reviewed journals between the years 2013 and 2018. Articles were selected based on their relevance to my clinical question and if they included patient-oriented outcomes. Inclusion criteria included randomized control trials published after 2008 and studies evaluating osteoarthritis and phonophoresis using NSAIDs. Exclusion criteria included articles published in 2008 or earlier. Statistics reported include p-value and mean change from baseline.

OUTCOMES MEASURED

Outcomes were measured using a visual analog scale, where pain severity was self-reported by patients across a continuum on a scale of 0-100; 0 representing no pain at all and 100 representing the worst pain imaginable. The VAS was completed at baseline and after two weeks of treatment to assess efficacy of the intervention compared to the control group. Outcomes were measured 2 days after the final treatment session to avoid short-term effects of heat application.[1] Additionally, the study completed by Oktayoglu et al.[3] included further follow up at one, two, and three months post-treatment to evaluate longer term effects of treatment intervention.

Table 1: Demographics and characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Luksurapan[1] (2013)	Double blind RCT	46	26-78	All patients fulfilled American College of Rheumatology criteria for knee OA, Kellgren and Lawrence scores between I-III, VAS score $\geq$ 50	Knee pain not due to OA, chronic systemic inflammatory diseases, allergy to piroxicam, recent knee injury or surgery, using NSAIDs, corticosteroids, or tramadol hydrochloride	0	Continuous Phonophoresis with piroxicam gel for the duration of 10 minutes, 5 times a week for 2 weeks. Ultrasonic wave frequency of 1 MHz and power of 1 W/cm^2
Monisha[2] (2018)	Double blind RCT	50	40-70	Age 40-70, Baseline VAS score of 10	Knee pain not due to OA, chronic systemic inflammatory diseases, allergy to piroxicam, history of knee injury or surgery, VAS score < 10, using NSAIDs or corticosteroids	0	Continuous Phonophoresis with piroxicam gel for the duration of 10 minutes, 5 times a week for 2 weeks. Ultrasonic wave frequency of 1 MHz and power of 1 W/cm^2
Oktayoglu[3] (2014)	Prospective RCT	40	54.55 $\pm$ 8.6	All patients fulfilled American College of Rheumatology criteria for knee OA, Kellgren and Lawrence scores between II-IV, VAS score > 50 with either walking, knee flexion, or resting	Secondary OA, intraarticular or intramuscular corticosteroids, intraarticular hyaluronic acid in the past 3 months, allergy to NSAIDs, physical therapy in the past 6 months, systemic or malignant diseases, abnormal lab results, dermatological problems, using NSAIDs or other analgesic drugs	0	Continuous Phonophoresis with diclofenac diethylamonium gel for the duration of 10 minutes, 5 times a week for 2 weeks. Ultrasonic wave frequency of 1 MHz and power of 1.5 W/cm^2

RESULTS

All three studies compared the efficacy of continuous phonophoresis with an NSAID based gel, either piroxicam or diclofenac diethylamonium, to nonpharmacologic ultrasound gel. Phonophoresis was generally well tolerated, without reports of any serious side effects. A total of 10 sessions were completed, five times a week for two consecutive weeks for the duration of 10 minutes each session. Studies conducted by Luksurapan et al. and Monisha et al. used ultrasonic wave frequency of 1 MHz and power of 1 W/cm^2, whereas the study conducted by Oktayoglu et al. used a wave frequency of 1 MHz and power of 1.5 W/cm^2.[1,2,3] All three studies used the visual analog scale to evaluate a mean change from baseline and to obtain a P-value to determine statistical significance of phonophoresis compared to ultrasound in OA pain reduction.

The first study conducted by Luksurapan et al. was a double blind randomized controlled trial consisting of 45 females and 1 male between the ages of 26 and 78, with a median age of 59 years.[1] Each group being studied consisted of 23 individuals that fulfilled the American College of Rheumatology criteria for knee OA, Kellgren and Lawrence scores between I-III, and a VAS score $\geq$ 50.[1] Exclusion criteria is listed in Table 1. There were no significant differences between each group in terms of duration of knee pain, hours of weight-bearing activity, or Kellgren-Lawrence scores.[1] All participants in both study groups completed their allocated treatment without any dropouts.[1] Everyone in the phonophoresis group completed all 10 treatment sessions, whereas 2 individuals in the ultrasound group completed 7 and 9 of the 10 treatment sessions.[1] ANCOVA was used to adjust for the imbalance of treatment sessions attended.[1] Patients in the phonophoresis group received 20 mg of 0.5% piroxicam gel, whereas standard coupling gel was used in the control group.[1] As seen in Table 2, both groups showed significant change in their VAS scores, indicating decreased OA knee pain.[1] The phonophoresis group

presented with a significant reduction of pain and a mean change from baseline of 67% compared to the control group receiving ultrasound, with a mean change from baseline of 39%.[1] The mean of between group difference was 14.73 +/- 5.78 with a p-value of 0.009.[1] While this data shows strong statistical significance, there is a wide 95% confidence interval (5.99-30.27), which may indicate a less precise estimate of the treatment effect due to a small sample size.[1]

Table 2: Mean Change from Baseline and Statistical Significance, Luksurapan[1]

	Baseline	**Post-Treatment**	**Mean Change from Baseline**	**P-value**
Phonophoresis	70.57 +/- 12.03	23.57 +/- 19.27	67%	0.009
Ultrasound	72.48 +/- 12.33	43.91 +/- 25.19	39%	

The second study conducted by Monisha et al. was a double blind randomized controlled trial consisting of a total of 50 women between the ages of 40 and 70 years.[2] Participants were randomly allocated to 3 different treatment groups, two of which are the focus of this review.[2] One group received phonophoresis with piroxicam gel and standard coupling gel in a 4:10 ratio, whereas the control group received ultrasound with an aquasonic gel.[2] There was no mention of the number of individuals allocated to each treatment group or if there were any dropouts over the duration of this study. Inclusion criteria included a baseline VAS score of at least 10 and exclusion criteria is listed in Table 1. VAS scores of both groups, demonstrated in Table 3, show an improvement of mild to moderate OA knee pain when compared to baseline scores. The phonophoresis group showed a significant improvement of knee pain with a mean change from baseline of 70%, compared to the ultrasound group which showed a mean change from baseline of 50%.[2] The p-value reported in this study was ≤ 0.00, which indicates a strong statistical significance.[2]

Table 3: Mean Change from Baseline and Statistical Significance, Monisha[2]

	Baseline	Post-Treatment	Mean Change from Baseline	P-value
Phonophoresis	75	25	70%	$\leq$ 0.00
Ultrasound	73	50	50%	

The third study conducted by Oktayoglu et al. was a prospective randomized controlled trial consisting of 40 participants, 10 men and 30 women.[3] The phonophoresis group consisted of 13 women and 7 men with an average age of 54.55 +/- 8.65 years, whereas the ultrasound group consisted of 17 women and 3 men with an average age of 55.05 +/- 10.08 years.[3] A non-treating author randomly allocated participants into each group, however there was no mention on whether or not patients, clinicians, and study workers were kept blind to treatment.[3] All participants fulfilled the American College of Rheumatology criteria for knee osteoarthritis, had Kellgren-Lawrence scores between II-IV and VAS scores above 50.[3] Exclusion criteria is listed in Table 1. There was not a significant difference in demographic data or pre-trial clinical parameters between the two study groups.[3] The phonophoresis group received 1.16% diclofenac diethylamonium gel and the ultrasound group received a nonpharmacologic acoustic gel.[3] VAS scores of walking, resting and flexion movement were obtained at baseline, post-treatment at 2 weeks, and at one, two, and three months following treatment.[3] There was no mention of dropouts over the duration of this study. For the purpose of this review, data in Table 4 presents walking VAS scores. As seen in Table 4, improvements were examined in VAS scores in both the phonophoresis and ultrasound groups during all follow up times.[3] Both groups had comparable VAS scores from baseline to post-treatment at 2 weeks.[3] At one month follow up, the phonophoresis group was shown to be superior to the ultrasound group when comparing

walking VAS scores, with a mean change from baseline of 23 compared to 10, respectively.[3] Statistical significance is demonstrated with a p-value of less than 0.05.[3]

Table 4: Mean Change from Baseline and Statistical Significance, Oktayoglu[3]

	Baseline	Post-Treatment	1 month follow up	2 month follow up	3 month follow up
Phonophoresis	64.5 +/- 14.68	52 +/- 12.81 P-value: 0.002	41.5 +/- 19.8 P-value: 0.001	47 +/- 22.73 P-value: 0.002	47.74 +/- 19.89 P-value: 0.003
Ultrasound	61 +/- 13.72	50 +/- 11.23 P-value: 0.001	51 +/- 11.19 P-value: 0.003	52.5 +/- 7.86 P-value: 0.007	53.5 +/- 9.33 P-value: 0.024

DISCUSSION

The objective of this systematic EBM review is to determine whether or not phonophoresis using NSAIDs reduces osteoarthritis knee pain. Each study used a visual analog scale to evaluate pain at baseline and after two weeks of treatment with either phonophoresis or nonpharmacologic ultrasound. Each study measured VAS outcomes two days after completion of treatment to avoid any short-term effects of heat application.[1,2,3] The study conducted by Oktayoglu et al. additionally examined one, two, and three months follow up of treatment. This study showed promising results at one month follow up, but additional studies are needed to further evaluate long term effects of phonophoresis and to determine appropriate frequency of treatment. While this treatment option may be relatively inexpensive and well tolerated, there may be issues with poor compliance if patients are required to be present for treatment 5 days a week for two consecutive weeks. Phonophoresis should be administered for at least 10 minutes each session, as shorter application times have been proven to be ineffective.[8] This may be a limitation to providers who do not have sufficient time or personnel to help administer this treatment effectively.

Phonophoresis is noninvasive and simple to administer, which makes this treatment modality a great option for both patients and providers. While OA affects a wide range of patients, phonophoresis could be used in a variety of primary care settings, and not limited to physical therapy clinics. The sample size in all three studies ranged from 40-50 participants, which is relatively small. Evaluating larger experimental groups may be beneficial in assessing outcomes, as outliers in the study will not affect the results as much as they do in smaller sample sizes. The study conducted by Monisha et al. only examined female patients and the studies conducted by Luksurapan et al. and Oktayoglu et al. were female predominant. Studies have shown that male and female responses to treatment of pain may differ, indicating that the studies being reviewed in this paper may not have the ability to generalize these results to the general population.[1]

Phonophoresis may be used to enhance transcutaneous delivery of NSAIDs to block nociceptive and neuropathic pain.[8] One study determined that diclofenac had the smallest flow and permeability, when compared to ibuprofen 5% and piroxicam, making it more efficacious in pain reduction.[8] Additional studies may be needed to determine which NSAID should be used to achieve maximum absorption and effectiveness. It may also be beneficial to have additional studies to compare outcomes using the same type of NSAID gel for phonophoresis in each experimental group. Luksurapan et al. and Monisha et al. used different ultrasound parameters in terms of power when compared to Oktayoglu et al., which could also facilitate different results in terms of percutaneous drug diffusion.[1] Standardization of ultrasound wave frequency and power would help make these studies more comparable.

According to the Food and Drug Administration (FDA), ultrasonic therapy devices must comply with medical device regulations and radiation safety performance standards, although

phonophoresis and ultrasonic diathermy devices have not been formally evaluated and approved.[11] Phonophoresis is still considered experimental and investigational by insurance companies, which may limit coverage of this treatment and become a financial barrier to some patients.

Diclofenac gel is an approved treatment option for acute pain, osteoarthritis, and actinic keratosis.[9] Skin irritation, including pruritis, contact dermatitis, application site pain, and desquamation, is a frequently reported side effect of this medication.[9] Topical diclofenac gel is contraindicated in those with hypersensitivity to diclofenac or history of asthma, urticaria, or other allergic reactions to NSAIDs, open skin wounds, infections, or damaged skin.[9] Other possible adverse reactions of topical diclofenac gel may include elevated liver function enzymes, gastrointestinal upset, and central nervous system effects such as headache, paresthesia, and hyperesthesia.[9] Black box warnings for topical diclofenac include cardiovascular thrombotic events, gastrointestinal bleeding, ulceration, and perforation, although these risks are significantly lower than use of oral NSAIDs.[6,9] NSAIDs should be avoided starting at 30 weeks of pregnancy due to risk of premature closure of fetal ductus arteriosus, although topical application of diclofenac crosses the placenta to a lesser extent than systemic use.[9] It is unknown on whether or not use of topical diclofenac will be detected in breast milk, whereas it may be present with systemic use.[9] Less information is given specifically for topical piroxicam, although breastfeeding is not recommended.[10]

CONCLUSION

All three studies demonstrated conclusive evidence in short-term reduction of mild to moderate osteoarthritis knee pain with the use of phonophoresis using NSAIDs. Additional studies should to be completed to address limitations as mentioned and obtain more data

regarding this topic of study. Future experimental trials may benefit from evaluating treatment response from larger study groups and more diverse patient populations in terms of gender. From a clinical standpoint, it may also be beneficial to evaluate longer term effects of treatment. When non-pharmacological treatment options have failed or are no longer an option, oral NSAIDs, intraarticular steroids, and surgery are still some of the most commonly used treatments. Enhancing topical NSAID absorption via phonophoresis may be a great, safe alternative treatment option.

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