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Efficacy of combined local mechanical vibrations, continuous passive motion and thermotherapy in the management of osteoarthritis of the knee

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Summary

Objectives: We evaluated the efficacy of combined mechanical vibrations, continuous passive motion (CPM) and heat on the severity of pain in management of osteoarthritis of the knee (OA-K).

Methods: In this controlled, double crossover study, 71 OA-K patients were randomized in Phase 1 to receive 4 weeks active treatment consisting of two 20-min sessions per day (34 patients, Group AB) or treatment with a sham device (37 patients, Group BA). This was followed by a 2-week washout period (Phase 2). In Phase 3, patients crossed over so that Group AB was treated with the sham device and Group BA received active treatment for an additional 4 weeks. Patient assessments of pain (visual analog scale, VAS) and Western Ontario and McMaster Universities (WOMAC) OA index were performed at baseline and at study weeks 2, 4, 6, and 10. Net treatment effects were estimated by comparing outcomes between active and sham treatment study phases.

Results: Treatment benefits were noted for both of the trial's two pre-specified primary endpoints, VAS and WOMAC. VAS was reduced at all follow-up time points for patients receiving active treatment compared to sham treatment with a net treatment effect of 14.4 ± 4.1 mm ($P = 0.001$). Similarly, the WOMAC score was reduced significantly with active treatment at all measured points with a net effect of 8.8 ± 1.9 points ($P < 0.001$). The secondary endpoints, range of motion (ROM) and treatment satisfaction, also improved with active vs sham treatment.

Conclusion: Four weeks treatment with combined CPM, vibration and local heating significantly decreases pain, improves ROM and the quality of life in patients with OA-K (ClinicalTrials.gov registration number: NCT00858416).

Key words: Osteoarthritis, Heat therapy, Vibration therapy, Continuous passive motion.

Introduction

Osteoarthritis (OA) is the most common form of joint disease worldwide, affecting 21 million adults in the United States alone. In addition to pain, OA poses serious health problems due to immobility, side effects of medications and joint-related surgery complications. Currently accepted treatment options for OA include patient education, weight loss, physical rehabilitation, exercise[1,2], modification of activities of daily living, food supplements and pharmacotherapy. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most widely used pharmacologic treatment, but provide incomplete effectiveness and can cause serious side effects[3–5]. Non-pharmacologic measures such as weight loss and adjusting physical activity are recommended by all therapeutic guidelines and are aggressively promoted by public health institutions. Unfortunately, compliance, especially over long periods of time, limits the effectiveness of these modalities[6]. Since there is no accepted structure (disease) modifying therapy, the primary goals of contemporary therapy are to reduce pain, improve joint function and improve quality of life.

The role of various non-pharmacological therapies has been investigated in the treatment of pain and as components of physical rehabilitation in different orthopedic conditions, though not all of the available approaches have been specifically tested for treatment of osteoarthritis of the knee (OA-K)[7]. For example, continuous passive motion (CPM) has been investigated extensively in the setting of recovery from total knee arthroplasty[8–10] but not specifically for OA, although there have been some studies testing active and passive joint movement and muscle contraction[7]. Vibration therapy has been tested for treatment of various types of pain[11,12] but not for OA[7]. Local heat has been investigated for pain[13,14] and anecdotal reports have appeared for OA[15]. We hypothesized that combining these three modalities together would provide a significant degree of symptomatic relief with improved mobility. We elected to test a new device (Kineticure, Israel) that combines these three treatment modalities.

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Methods

PATIENTS

The study was a prospective, randomized, controlled, double crossover study involving a total of 71 patients enrolled from an outpatient orthopedic clinic at a single institution (Jacksonville Orthopedic Institute, Jacksonville, FL). The study was approved by the Schulman Associates IRB, Inc. acting on the authorization of the Baptist Medical Center, Jacksonville, FL with which the clinic is affiliated (IRB #06-1297-0, approved on March 29, 2006) and the study was conducted in compliance with the Helsinki Declaration. Patients were recruited between April 2006 and March 2007. Each patient provided informed consent prior to participation.

Consecutive patients were eligible for inclusion into the study if they were between 45 and 80 years of age, had a diagnosis of OA-K by American College of Rheumatology (ACR) criteria (with at least one osteophyte on X-ray)[16], had symptoms consistent with radiographic OA grades 2, 3 or 4 by Kellgren and Lawrence criteria, and had moderate to severe knee pain ($\geq$35 mm on a 100 mm visual analog pain scale (VAS)). Patients were also required to be ambulatory without assistance, be willing and able to participate in the treatment protocol and follow-up visits and be able and willing to provide informed consent. Patients were excluded from participation if they had knee or hip surgery (including joint replacement) in the limb to be treated at any time, if they had intra-articular visco-supplementation injections within 6 months, intra-articular corticosteroid injections within 2 months, signs or symptoms suggestive of a non-OA cause of knee pain or a painful ankle or hip in the same limb. Patients were also excluded if they had other diseases that could result in pain or physical limitation in the treated limb, change in pain medications (type, frequency and dosage), physiotherapy, acupuncture, natural remedies or use of orthotic devices within 2 weeks.

Following enrollment, patients were randomized into one of two groups: Group AB or Group BA. Randomizations were in blocks of 4. Randomization codes were concealed in sequentially numbered envelopes prepared by the sponsor that were stored at the site and opened by the study coordinator following each patient enrollment. The study was divided into three periods as summarized in Fig. 1. Phase 1 was a 4-week period in which Group AB patients received active treatment with the Kineticure device while Group BA patients were treated with a sham device (both devices described below). Phase 1 was followed by a 2-week "washout period (WO)" during which no treatments were administered (Phase 2). Study Phase 3 was a 4-week period in which Group BA patients received active treatment with the Kineticure device while Group AB patients were treated with the sham device. Thus, the duration of each subject's participation was 10 weeks. Patients were instructed not to alter other treatments (e.g., types and amounts of non-steroidal medications) that were present during the 2 weeks prior to enrollment and throughout the study duration; in cases where changes occurred that could have influenced outcomes, patients were withdrawn from the study (as detailed below).

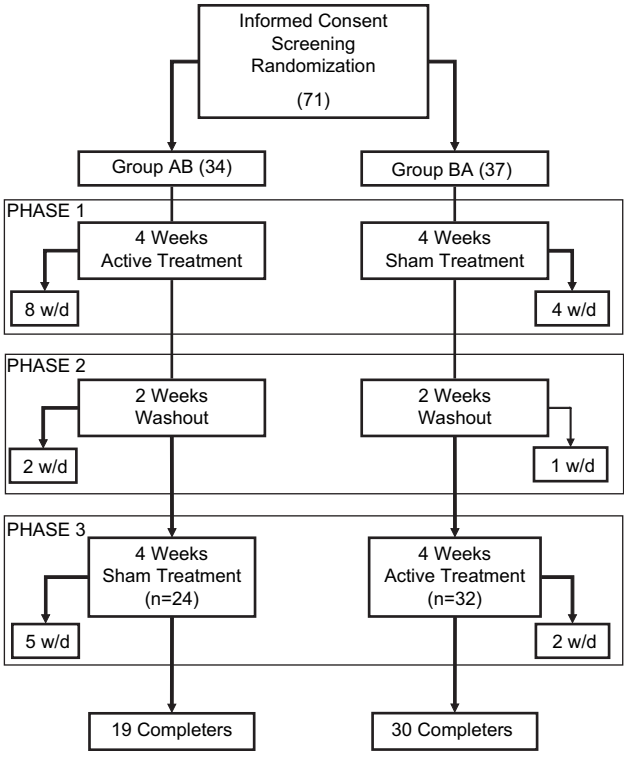

Fig. 1. Overview of this prospective, double crossover study. Numbers in parentheses show number of patients entering the various phases of the study. w/d, withdrawn from study (refer to Table II for reasons for w/d).

ACTIVE AND SHAM TREATMENTS

Although the study was not blinded to investigators, efforts were made to minimize bias with the use of a sham device. The active and sham devices looked identical. Patients were specifically not informed of the exact nature of the active treatment (other than it involved wearing a knee brace) or the differences between the active and sham devices.

Active treatment was provided by the Kineticure system 20 min per session, twice per day for 4 weeks. The system consists of a knee brace with integrated heating pad and vibration unit, and a foot pedal that delivers CPM (Fig. 2). The knee brace is composed of a stretchable textile support that is placed around the knee and a polyurethane case that houses the vibration motor, the batteries and a printed circuit board (that controls the vibration unit); a hinge in this casing allows for movement of the knee during CPM. The brace is held in place with an adjustable buckle strap above the knee and an adhesive strap below the knee that are integrated into the textile support, with the polyurethane case on the lateral side of the knee. The frequency of vibration is varied repeatedly over four 10-second periods: 10 s at 10 Hz, 10 s at 27 Hz, 10 s at 42 Hz and 10 s of no vibrations. Each treatment period, which lasts 20 m, therefore consists of 30 such cycles. As seen in Fig. 2, vibrations are transmitted to the leg just above and just below the knee through the polyurethane casing (which span a quarter to a third of the leg circumference in each location) and through the straps that extend around the entire leg at both locations. Heating is provided by a commercially available exothermic heating pad that is inserted into a pocket on the inner side of the textile support prior to each treatment. This heating pad attains temperatures of 40.0–40.5°C within 30 min of being activated by simply opening the package; patients are asked, therefore, instructed to active the pad 30 min prior to starting the treatment period. The temperature is maintained for the 2 h treatment periods. The foot pedal cycles through 45° every 10 s.

As already noted, the sham device looked the same as the active device, but consisted of a non-vibrating knee brace with no heating pads or foot pedal. As for periods of active treatment, patients were instructed to wear their knee brace twice a day for 20 min during the designated 4-week sham study periods.

OUTCOME MEASURES

The primary outcome measures of this study were intensity of pain as measured on a 100 mm non-marked VAS and the total Western Ontario and McMaster Universities (WOMAC) OA index using a Likert scale, with

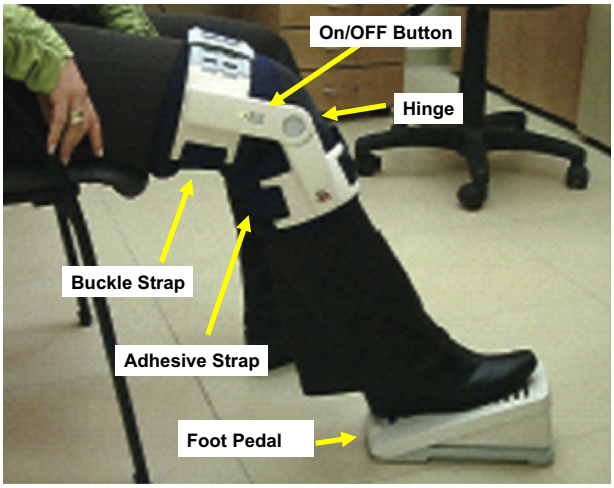

Fig. 2. Picture of the device will all its components as labeled.

scores ranging from 0 (no pain, no disability) to 96 (maximal disability and pain) points[17].

Secondary outcome measures of this study were VAS of satisfaction of use of the Kineticure device as measured on a 0–100 mm non-marked scale and range of motion (ROM) of the knee (using goniometer) and knee circumference, both measured by a trained investigator blinded to treatment group.

All parameters were measured prior to initiation of treatment, after providing the first treatment in the clinic to assess the immediate effect, and during follow-up visits to the clinic every 2 weeks. Treatments were not applied in the clinic on the days of the follow-up visits.

SAMPLE SIZE

Sample size was determined to ensure 90% power to detect a difference between active and sham treatments for each of the two co-primary endpoints of at least 0.9 standard deviation (SD) units based on two-tailed 0.025 level *t*-test. Based on these criteria, a total of 60 patients (30 in each group) are required. The trial randomized 11 additional patients (for a total of 71) in anticipation of a 15% drop out rate.

STATISTICAL ANALYSIS

Data from this crossover study were analyzed using a mixed model analysis of variance as described in Brown and Prescott[18]. Estimates of the treatment effect for each period were based on the difference between the baseline measurement and the end of period treatment measurement at 10 weeks post baseline. The significance of the treatment effect was based on a *t*-test, with degrees of freedom determined using Saterthwaite's approximation. Given that two co-primary endpoints were pre-specified, each test was conservatively conducted at a two-sided 0.025 level, in order to maintain an overall Type I error probability of 0.025. All analyses were conducted using PROC MIXED, version 9.1, SAS Institute Inc., Cary, NC.

Results

A total of 71 patients signed informed consent, passed baseline screening and were randomized between Group AB ($n = 34$) and Group BA ($n = 37$). The baseline characteristics of the patients for the two groups are summarized in Table I and show that randomization resulted in groups with similar characteristics (Table I). The overall flow of patients through the study is summarized in Fig. 1. A total of 22 patients dropped out at some point before the end of the study. Fifteen patients in Group AB dropped out during the study leaving 19 completed as compared to seven drop out patients in Group BA and 30 completed subjects. We could not identify a reason for the overall imbalance in dropouts between groups, resulting in a greater number of Group BA completes. Baseline demographic characteristics of patients who dropped out were similar to those of patients who remained in the study. Reasons for drop out by study group and study period are summarized in Table II. Eight patients were either unable or unwilling to comply with the schedule of study visits. Five patients had significant changes in pain medications and were dropped at the discretion of the Principal Investigator. Three patients dropped out during active treatment because they felt they were not deriving benefit, compared to one drop out for this reason during a period of sham treatment.

Table I
Baseline demographics and entry pain and stiffness scores

	Group AB sham treatment followed by active treatment (mean ± SD)	Group BA active treatment followed by sham treatment (mean ± SD)
Age (years)	64.1 ± 9.5	58.7 ± 8.2
Height (cm)	165.7 ± 10.1	169.5 ± 13.4
Weight (kg)	92.6 ± 19.4	99.6 ± 23.2
BMI	33.7 ± 6.6	34.7 ± 7.3
Men (%)	44.0%	48.6%
VAS for pain (mm)	70.4 ± 18.6	65.1 ± 17.4
WOMAC score		
Total	46.1 ± 14.2	44.1 ± 14.1
Pain	9.6 ± 2.9	10.5 ± 3.3
Stiffness	4.2 ± 1.4	4.6 ± 1.4
Physical function	32.2 ± 11.0	29.1 ± 1.8
ROM (°)	108 ± 21	106 ± 24

WOMAC, Western Ontario and McMaster Universities Likert scale. BMI, body mass index.

Overall, the device was well tolerated and easily used by most patients. There were no serious adverse events. The time courses of change of the primary and secondary endpoints are summarized in Figs. 2–5. Pain, quantified by the visual analog scale (VAS), significantly improved with active treatment compared with sham during both treatment periods. The net difference in change of VAS between active and sham treatments (calculated as detailed above) averaged 14.4 ± 4.1 VAS points ($P = 0.001$). Of note, active treatment resulted in significantly improved VAS during Phases III despite the fact that the Phases III active treatment group started with higher VAS. WOMAC improved significantly between active and sham treatment in both Phases 1 and 3 (average 8.8 ± 1.9 points, $P < 0.001$). Again, Phase 3 benefits were apparent despite an initial imbalance in WOMAC scores at the time of crossover between treatments. The pain stiffness and physical function dimensions of WOMAC each improved significantly with active treatment compared to sham treatment by 2.2, 1.1 and 6.0 points respectively ($P < 0.001$ for each parameter).

During study Phase 1, ROM showed no improvement with sham treatment, but improved significantly with active treatment. This improvement waned minimally during the WO and during the initial half of study Phase 3. For sham patients however, at the end of Phase 3, there were no differences between groups. Overall, the net treatment effect on ROM was 4.6 ± 1.9° ($P = 0.02$) during the entire study course.

Finally, there was a high degree of patient treatment satisfaction as judged immediately after the first treatment (Fig. 6). This occurred for both the sham (placebo effect) and active treatments. However, the degree of satisfaction was significantly great with the active treatment. Over time, satisfaction was maintained with active treatment, but waned with sham treatment. These same patterns emerged after crossover. The net treatment effect on satisfaction averaged 51 points ($P = 0.002$).

Table II
Reasons for discontinuation by group and study period

	Group AB		Group BA	
	Active + WO	Sham	Active	Sham + WO
Went to surgery		1		
Not deriving benefit	2	1	1	
Device uncomfortable	1			
Device inconvenient				1
Too difficult to operate device	1			
Change of medications	2	1		2
Unable or unwilling to return to clinic	4	2		2
Unrelated intercurrent injury			1	

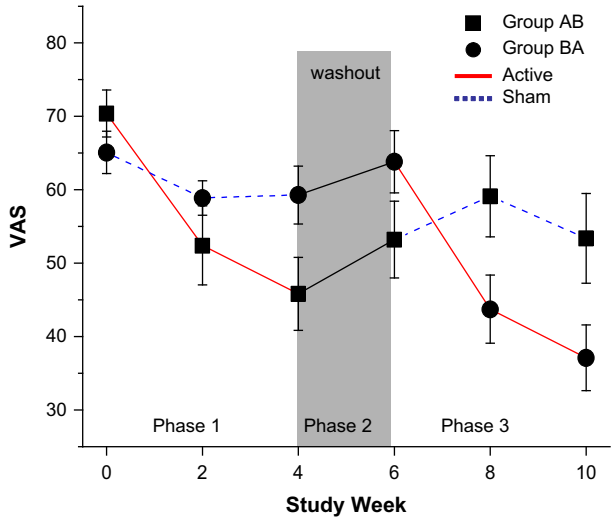

Fig. 3. Changes in visual analog scale (VAS) of pain (in units of millimeters) as a function of group and phase of study. See text for details.

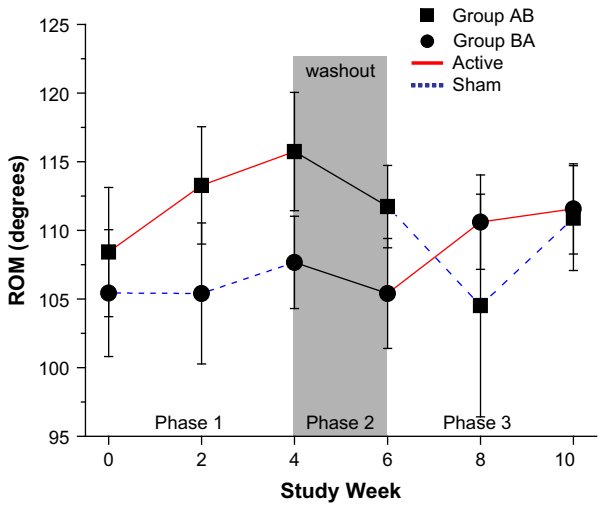

Fig. 5. Changes in ROM as a function of group and phase of study. See text for details.

Discussion

In a prospective, controlled, double crossover study, patients with OA-K were treated in 4-week cycles with a system that combines vibration, local heat and passive motion. When compared to a sham treatment, active treatment significantly reduced pain, reduced stiffness and improved physical function as measured by VAS and WOMAC subscale scores. Secondary measures also improved as measured by ROM and degree of treatment satisfaction. No adverse effects were reported during the 4-week treatment period.

Concern over side effects of NSAIDs has led patients to seek, and investigators to develop, alternative treatments. For example, two prior reports showed that moderate exercise may improve joint symptoms and function OA-K[19,20]. A different approach tested the effectiveness of acupuncture over 26 weeks. That study showed significantly improved pain score (40% decrease from baseline)[21]. Our results show decrease in pain in a similar range (39% from baseline). Yet another category of treatment for OA are braces and neoprene sleeve knee supports. In clinical trials, when compared to medical treatment, it has been shown that these devices have limited additional beneficial effect for pain and function in OA-K[22].

Prior studies have examined CPM[8–10], vibration[11,12] and heat[13,14] separately for treatment of pain in various orthopedic conditions, though not specifically in OA-K[7,15]. CPM is indicated in post-total knee replacement therapy, with proven benefits in improving mobility, ROM and functionality. Limitations of CPM are inconvenience and substantial costs. Vibration therapy is known to have many different physiologic and therapeutic effects depending on its acceleration, amplitude, frequency, length of exposure and method of application. In addition to reduced pain in

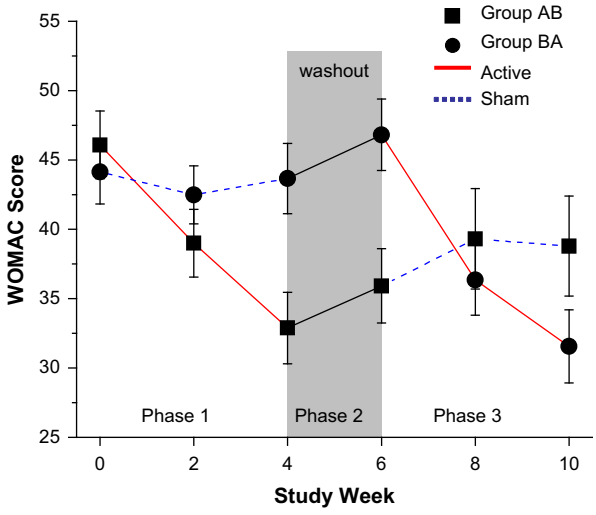

Fig. 4. Changes in WOMAC OA index using a Likert scale. See text for details.

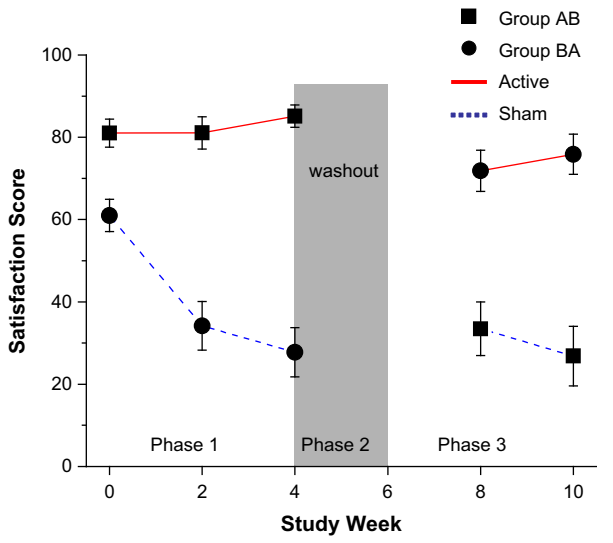

Fig. 6. Changes in treatment satisfaction measure on a visual scale (in units of millimeters) as a function of group and phase of study. See text for details.

a variety of settings[11,23–25], increased circulation (blood, lymph, other bodily fluids) has also been demonstrated[16,26]. In addition, microvascular filtration is shifted with vibration, producing a pronounced increase in the threshold for edema formation because lymphatic flow is increased[24]. Vibration also activates cell surface motion-receptors and influences cellular functions such as growth-rate and substance production such as proteoglycan[27,28]. Vibration treatment also improves muscle force through mechanisms such as the tonic vibration reflex, improved nerve-muscle function, realignment of muscle fibers and increased substance production by secretory cells[29–33]. Vibration has also been shown to be helpful in some aspects of pain management[11,12,34]. On the other hand, it is known from studies of both experimental animals[35] and humans[36] that vibration can stimulate bone formation. If, in the long term, this stimulates osteophyte growth or leads to stiffening of the subchondral cansellous bone, there could be negative consequences on pain and overall outcome[37].

Two forms of heat therapy are available. Superficially applied treatments, 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[38]. However, in a systemic review of the literature, treatment with hot packs did not demonstrate any significant beneficial effect when used to treat OA[38].

Although the present study was under powered to definitively prove safety, no adverse events or ill effects were reported in this study. It is interesting to note that regulatory bodies such as Occupational Safety and Health Administration (OSHA) and the International Organization for Standardization (ISO) discuss potential health issues arising from chronic exposure to vibration. Although they do not specifically comment on standards for vibration exposure to the knee, they do provide guidance for hand and wrist, as well as whole body exposure. These standards provide limits and boundaries for vibration exposures over an 8 h per day and provide values of 5 m/s^2 for the hand and 9 m/s^2 for the entire body. Assuming an amplitude of vibration provided by the Kineticure device on the order of 0.1 mm (which we take as an over estimate), the acceleration provided at the maximum frequency would be approximately 7 m/s^2. Given that this value is less than the boundary set for the whole body exposure and that the duration of vibration application is less than 40 min per day (i.e., two 20-min sessions, with ¼ of the time without vibrations), this level of exposure, based on these standards, is markedly less than would be expected to cause any untoward effects, even during chronic daily use over long periods of time.

Limitation of the present study include the limited number of participants, the relatively short treatment period and the unblinded nature of the study. Hence, it would be important to study a longer treatment period to examine durability of response. Although efforts were made to minimize placebo effect (e.g., use of a sham device, minimal information provided to patients about the nature of the treatment and use of investigators blinded to treatment group to conduct evaluations), it is recognized that patients could not be blinded to the nature of the treatment. Accordingly, the true impact on pain and motion could be less than the current results indicate. This would even include ROM measurements which, in the absence of a validation of measurement reproducibility and objectivity, could have been influenced by investigator bias. It would also be interesting to consider the residual effect (i.e., how long the benefit last after the therapy discontinued) achieved with this device. It would be interesting to investigate durability of the effect in light of findings noted above in experimental animals and humans that vibration may bone formation which could have negative consequences in the setting of OA. As seen in Figs. 2–5, outcome measures did not return to baseline by the end of the WO following the first treatment period. Suggesting the duration of residual effect of a 4 weeks treatment course is more than 2 weeks. Another limitation of the study was the relatively high drop out rate; the drop out was largely because patient noncompliance with the study visit schedule and because of changes in pain medications which would have interfered with interpretation of the findings. Finally, we measured the impact of simultaneous heat, vibration and passive motion treatment; therefore we cannot determine the relative contributions of each of the three components to the overall treatment effects.

The strengths of the present study are that this is the first time that combined treatment with CPM, vibration and local heating for OA-K has been investigated and shown to have a beneficial effect on pain and quality of life, along with ROM improvement following 4 weeks of treatment. The crossover study design, considered to be the best for evaluating treatment modalities in OA, also allowed for collection of efficacy data in a larger number of patients.

Conclusions

In this double crossover study, 4 weeks of treatment with combined CPM, vibration and local heating significantly improved pain, quality of life and ROM in patients with OA-K. In addition, the treatment appears to be safe (at least during 4-week treatment period) and, along with its demonstrated efficacy, provides an attractive primary or adjunctive treatment for this condition[39].

Conflict of interest

This study was supported by Kineticure, Inc. Helfet DL and Markenson JA are paid consultants to Kineticure.

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