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A Cetylated Fatty Acid Topical Cream with Menthol Reduces Pain and Improves Functional Performance in Patients with Arthritis

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ABSTRACT

This investigation was an extension of a previous study in our laboratory where we have shown one month of treatment with a topical cream consisting of cetylated fatty acids was effective for reducing pain and improving functional performance in patients with osteoarthritis (OA) of the knee (Kraemer et al., *Journal of Rheumatology*, 2004). We wanted to verify that the addition of menthol to the compound would produce a similar percent improvement in therapeutic effects. We used a single treatment group pre-post design to examine % treatment changes. Patients diagnosed with OA of the knee (*N* = 10; age = 66.4 ± 11.5 yrs), and severe pain (e.g., OA, rheumatoid arthritis) of the elbow (*N* = 8; age = 59.1 ± 18.2 yrs) and wrist (*N* = 10; age = 60.3 ± 16.8 yrs) were tested for pain and functional performance before and after one week of treatment with a topical cream consisting of cetylated fatty acids and menthol applied twice per day(Celadrin™; Imagenetix, Inc., San Diego, CA). In patients with knee OA, significant improvements in stair climbing ability (~12%), "up and go" performance (~12%), balance and strength (~16.5%), range of motion (~3.5%), and reductions in pain were observed. In patients with severe pain of the elbow and wrist, significant improvements in dynamic (~22 and 24.5%, respectively) and isometric (~33 and 42%, respectively) local muscular endurance, as well as a reduction in pain were observed. Neither group demonstrated significant changes in maximal grip strength or maximal force production. One week of treatment with a topical cream consisting of cetylated fatty acids and menthol was similarly effective for reducing pain and improving functional performance in patients with arthritis of the knee, elbow, and wrist. The percent changes were consistent with our prior work on the compound with out menthol. Further work is needed to determine the impact of menthol in such a cream. Nevertheless, our data supports the use of a topical cream consisting of cetylated fatty acids (with or without menthol) for enhancing the potential for exercise training in this patient population.

Key Indexing Terms: FATTY ACIDS, OSTEOARTHRITIS, PHYSICAL PERFORMANCE, QUALITY OF LIFE

INTRODUCTION

Osteoarthritis (OA) is a progressive, degenerative joint disease estimated to affect more than 21 million individuals in the United States (19). The most common symptoms are pain, stiffness, reduced joint range of motion, and limitations to normal activities of daily living such as getting up from a chair, walking, balance, and ascending/descending stairs (8,9,11,12,24). Due to the debilitating effects of OA, there is a need for alternative treatments that benefit patients with OA without harmful side effects. Important for strength and conditioning professionals such treatments would also enhance the ability of patients to exercise.

One potential treatment which has shown promise is the use of oral and/or a topical blend of cetylated fatty acids (10, 15). Cetylated monounsaturated fatty acids have been shown to provide protection against arthritis in rats (5) and have been shown to increase knee range of motion and reduce pain in patients with knee OA (10). We have recently reported that a topical cream consisting of a proprietary blend of cetylated fatty acids significantly reduced pain and improved physical function in patients with knee OA (15). In that study, we reported acute improvements in stair climbing ability, timed “up and go” performance, knee range of motion, and a reduction in pain within 30 min of the first treatment with this topical cream. Additional improvements were observed after 30 days (i.e., cream was applied twice per day) of treatment. However, we only examined patients with knee OA and the topical cream used was only in its developmental

stage. Recently, menthol has been added to this topical cream. Menthol has been shown to possess analgesic properties thereby reducing the sensation of pain (6). Therefore, the present investigation was an extension of our previous research (15). In this study, our purpose was to examine the effects of a topical cream consisting of cetylated fatty acids, along with the addition of menthol, on pain and functional performance in patients with knee OA over the course of one week. In addition, we recruited several patients with severe pain (e.g., diagnosed with either OA or rheumatoid arthritis) of the elbow and wrist to examine potential effects on upper-extremity performance (3).

MATERIALS AND METHODS

Experimental Approach to the Problem

This study was part of a much larger investigation. Using a placebo-controlled, double-blind study, we have recently shown the benefits of treatment with a topical cream consisting of a blend of cetylated fatty acids (Celadrin^{TM}; Imagenetix, Inc., San Diego, CA) (15). Thus, the purpose of the present study was to extend the findings of our previous research and provide further support for the use of cetylated fatty acids (i.e., and the addition of menthol) in treatment of arthritis. In order to examine the primary hypothesis of the present investigation, patients diagnosed with arthritis by a physician were assigned to an experimental group based upon the anatomical location (i.e., knee, elbow, or wrist). Each patient applied the cream to the affected area twice per day every

day for one week and subsequently returned to the lab for post-study functional performance testing. The testing protocols consisted of assessments for pain, stiffness, knee range of motion (ROM), postural stability, balance, and ability to rise from a chair, walk, and ascend/descend stairs for patients with knee OA. We measured of grip strength, elbow ROM, dynamic and isometric muscle strength and endurance, and pain in patients with severe elbow and wrist pain. Due to the significant improvements observed in our previous investigation with use of a topical cream consisting of a blend of cetylated fatty acids (15) (i.e., as well as the lack of significant changes occurring in a control group using a placebo cream) and the high test-retest reliability (Intra-class correlation coefficients of *R* = 0.95 to 0.99) obtained with our assessments, our study design did not include a control group for this short extension of our previous research which was done to see if improvements did occur in a similar magnitude as with the topic cream that did not contain the menthol. A pre-post treatment design was used as control data had shown no improvements in the measures. Thus, future research will need to directly determine the effects of menthol alone on the associated measures used in this study. It must be clear that the impact of menthol cannot be determined with the current experimental design.

Patients and Consent.

All patients selected for the present study were recruited in conjunction with local physicians. Each participant was informed of the benefits and risks of the investigation and subsequently signed an approved consent form in

accordance with the guidelines of the university's Institutional Review Board for use of human subjects. Arthritis was diagnosed by the treating physicians and 28 patients (26 women and 2 men) were assigned to one of three groups: knee (*N* = 10), elbow (*N* = 8), or wrist (*N* = 10) arthritis. Patient demographics were: 1) knee: age = 66.4 ± 11.6 yrs; height = 162. 4 ± 6.4 cm; body mass = 83.5 ± 18.4 kg; years with arthritis = 8.8 ± 7.0 yrs, 2) elbow: age = 59.1 ± 18.2 yrs; height = 158.9 ± 7.6 cm; body mass = 76.8 ± 13.4 kg; years with arthritis = 5.9 ± 7.0 yrs, and 3) wrist: age = 60.3 ± 16.8 yrs; height = 159. 1 ± 6.7 cm; body mass = 74.7 ± 14.4 kg; years with arthritis = 4.9 ± 5.8 yrs.

Functional Mobility Measures.

Patients were assessed for functional performance before and following the seven-day experimental period. For patients with knee arthritis, the selection of assessments and the sequence performed was: 1) the timed "up-and-go", 2) stair-climbing test, 3) unilateral anterior reach, and 4) the medial step-down test. For patients with elbow and wrist arthritis, the selection of assessments and sequence performed was: 1) grip strength, 2) peak isometric force of the elbow flexors at 90^{o}, 3) one-repetition maximum (1 RM) of the elbow flexors, 4) isometric local muscular endurance of the elbow flexors at 90^{o}, and 5) number of repetitions performed for the arm curl with a standard resistance. All patients participated in two familiarization sessions prior to initiating the study. All tests were administered by the same investigator to ensure standardization of the

procedures and test-retest intra-class correlations producing reliabilities for all of the tests ranging from Rs = 0.95 to 0.99.

Lower-Extremity Assessments. The timed up-and-go test was performed using standard procedures (23). The patient sat in a standard arm chair. On the verbal signal “go” each patient ascended from the chair, walked until he/she crossed a tape marker located 3m away, turned around, walked back toward the chair and sat down. For the stair-climbing test, each patient ascended and descended a flight of eleven 13.5 cm steps as quickly as possible. The total, ascending, and descending times were recorded. For the unilateral anterior *reach*, each patient (with the hands positioned on the hips) extended a leg out as far as possible (while balancing on the opposite leg) over a standard tape measure while keeping the anterior foot close to the floor without touching. Three trials were given per assessment with the best score recorded for analysis. For the *medial step-down test*, each patient stepped down medially (from a 11.4 cm step) until the heel of the front foot lightly touched the floor and then returned to starting position (15). One trial was performed per leg with each patient volitionally performing as many repetitions as possible.

Upper-Extremity Assessments. Maximal grip strength for each hand was assessed with a hand-grip dynamometer. *Peak* isometric force of the elbow flexors was assessed using a linear-movement resistance exercise machine in conjunction with a force plate (Kistler Instrument Corporation, Amherst, NY). The

resistance bar was set for each patient to correspond to an elbow angle of 90^{o} (measured with a plastic goniometer) and was loaded such that no movement of the bar was permitted once adjusted to proper position. Each patient exerted maximal isometric force to the bar and the subsequent ground reaction force was recorded. Hand and foot positions were standardized and marked for each testing session. Using the same resistance exercise machine, the 1 RM arm curl was assessed. Each patient began with the elbows fully extended and proceeded to lift the bar in a full range of motion. Increments of 2.5 kg were added to each set until the patient could no longer complete a full repetition. For the isometric endurance assessment, patients were positioned in the resistance exercise machine (identical to the peak isometric force assessment) with hands placed on the bar at an elbow angle of 90^{o}. A standard resistance of 50-60% of patients' pre-study 1 RM was added to the bar and each patient was instructed to hold the weight at this position for as long as possible. Patient fatigue and/or failure to maintain the proper elbow and wrist position were criteria for test termination. The total time the patient was able to maintain this position was recorded. For the dynamic muscular endurance assessment, a standard dumbbell was used (e.g., 5.5 kg for men, 3.6 kg for women) for the unilateral arm curl exercise. Each patient performed as many repetitions as possible with each arm in a full ROM. All testing was conducted by a certified strength and conditioning specialist who used great caution when monitoring patient performance.

Clinical Assessment

Patients were assessed on basic clinical ROM of the knees (i.e., for those with knee OA) and elbow (i.e., for those with elbow arthritis). For knee ROM, patients were asked to lie supine with both legs fully extended. Patients were then asked to flex each knee as far as possible until discomfort. The knee joint angle was measured in both the supine extended and flexed positions using a standard goniometer. Similar procedures were used to measure the fully extended and flexed positions at the elbow joint while the patient was standing. The same investigator performed all measurements, which yielded test-retest reliabilities of 0.99 for both assessments. Pain, stiffness, and physical function of the lower extremities was assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (2, 22). For patients with elbow and wrist arthritis, a 0 (no pain) to 4 (extreme pain) pain scale was used similar to that of the WOMAC.

Topical Cream and Application

The topical cream used was a proprietary blend of cetylated fatty acid oil (cetyl myristoleate, cetyl myristate, cetyl palmitoleate, cetyl laureate, cetyl palmitate, and cetyl oleate), PEG-100, stearate, benzyl alcohol, lecithin, carbomer, potassium hydroxide, tocopheryl acetate, menthol, and olive oil (Celadrin^{TM}; Imagenetix, Inc., San Diego, CA). Patients were instructed to apply a standardized amount of cream to the affected area. Daily logs were completed to assure 100% compliance. In addition, patients were not taking additional

arthritis medications, did not initiate any exercise programs, and were not permitted to practice the performance tests to prevent any training effects during the one-week experimental period.

Statistical Analyses

Statistical evaluation of all data was accomplished using a paired T-test with alpha level corrections. Statistical power for the various dependent variables was determined to be 0.80-0.85 for the sample size used at the 0.05 alpha level (nQuery Advisor® software, Statistical Solutions, Saugus, MA). Significance was set at $P \leq 0.05$.

RESULTS

The results of this study are presented in Tables 1, 2, and 3. For patients with knee OA, there were significant reductions in the times to complete the up-and-go and stair climbing tests ($P \leq 0.05$). Unilateral anterior reach performance increased significantly whereas only a trend for improvement was observed for the medial step-down. Range of motion of the knee improved significantly during knee flexion, as well as during full extension for the left leg. WOMAC scales revealed significant reductions in pain and improvement in physical function. For patients with elbow and wrist arthritis, significant improvements were observed only in the local muscular endurance assessments (i.e., isometric endurance test and repetitions of the arm curl). No differences were observed in any strength or ROM measurements. In addition, perception of pain was reduced.

Tables 1, 2, and 3 about here

DISCUSSION

The findings of the present study support our previous research indicating that a topical cream consisting of a blend of cetylated fatty acids is effective for: 1) improving knee ROM; 2) improving ability to climb stairs, rise from a chair, and walk; and 3) improving balance, strength, and endurance in patients with knee OA. Unique to the present investigation was the findings that this topical cream also enhances dynamic and isometric local muscular endurance and reduces pain in patients with severe pain of the elbow and wrist (e.g., OA or rheumatoid arthritis).

The release of pro-inflammatory cytokines (e.g., interleukin-1ß and tumor necrosis factor-α) is an important mediator of inflammation. Fatty acids have been proposed to reduce chronic inflammation in patients with arthritis by reducing leukotriene B4 from stimulated neutrophils and of interleukin-1 monocytes (4,17). Other suggested mechanisms for the anti-inflammatory response are reduced expression and activity of proteoglycan degrading enzymes and cytokines, suppression of leukocyte function, changes in adhesion molecule expression and apoptosis triggering, and alterations in signal transduction and membrane fluidity (4,16,17). Cetylated monounsaturated fatty acids have been shown to provide protection against arthritis in rats (5) and increase knee ROM and reduced pain in patients with OA (10). Although the

mechanisms remain to be elucidated, our results support the use of topically-applied cetylated fatty acids in treatment of arthritis.

Functional performance is limited in patients with OA (14). Patients with knee OA have been shown to walk, ascend, and descend stairs with less velocity than healthy individuals (14). In addition, balance is limited partially due to strength reductions (8) and the ability to rise from a chair and walk is another functional performance task that is limited in patients with knee OA (12). Inactivity associated with OA pain results in further loss of muscle strength, power, and endurance in the upper and lower extremities that results in decrements in an individual's quality of life. The results of the present investigation, as well as our previous research (15), demonstrate the efficacy of a topical cream consisting of cetylated fatty acids for reducing pain and improving physical function. Improved ability to ascend/descend stairs, rise out of chair and walk, greater knee ROM, enhanced balance, and reduced pain were observed after only one week of treatment in the present study. It is interesting to note that some of these improvements may occur 30 min following the first treatment (15). The largest improvements in physical function observed in the present study was in our lower-extremity assessments. These data indicate that OA of the lower extremity may have more detrimental effects to physical performance involving weight-bearing activities.

Few studies have examined various topical treatments for improving performance and reducing pain in individuals with arthritis of the elbow or wrist. Most studies have investigated non-surgical treatments such as analgesics, nonsteroidal anti-inflammatory drugs, glucosamine, and chondroitin sulfate supplementation (21,26). Although effective, side effects may occur with chronic use of analgesics and NSAIDs (26). Thus, the development of topical treatments that produce no or minimal side effects is warranted. Recent studies have shown beneficial effects of herbal supplements and topical creams including capsaicin, piroxicam gel, articulin-F, willow bark, and phytodolor for reducing pain in patients with OA (21). Gemmell et al. (7) examined treatment with a topical cream consisting of several herbs in addition to capsaicin and menthol for 42 days and reported a 35-38% reduction in pain and stiffness in patients with OA of the hand and knee. The magnitude of pain reduction in that study was slightly greater than the average pain reductions reported with use of NSAIDs (i.e., 30%) (25). In the present study, we reported a ~43% reduction in pain in patients with arthritis of the wrist and elbow after only one week of treatment with a topical blend of cetylated fatty acids and menthol. Although our methodology for the assessment of pain differed from previous investigations, i.e., and direct comparisons can not be made, the results of the present investigation indicate favorable reductions in pain are possible with treatment of a topical cream consisting of a blend of cetylated fatty acids and menthol.

The measurement of hand grip strength has been used as one assessment of physical function in patients with severe pain in the hand and wrist. Grip strength has been shown to be compromised in patients with OA of the wrist (3) and hand (13). The reduction in grip strength has been mediated, in part, by pain and this reduction occurs in proportion to the severity of arthritis (13). Topical cream treatment (e.g., herbal formulas, capsaicin) periods of 1-3 months have had limited effects on grip strength in patients with arthritis despite reductions in pain (18,20). Our findings support these data as we did not report any changes in grip strength after only 1 week of treatment despite reductions in pain. Thus, it appears that other treatment modalities (i.e., exercise), in addition to treatment with a cetylated fatty acid/menthol topical cream, may be necessary to restore hand grip strength in patients with arthritis.

A unique aspect to the present investigation was our selection of assessments of local muscular endurance and strength in patients with severe elbow and wrist pain. No differences were observed in peak isometric or dynamic strength of the elbow flexors; however we did report significant improvements in local muscular endurance (e.g., dynamic repetitions completed and isometric time to exhaustion). It was not surprising that maximal muscle strength did not change. The present investigation was only one week in duration and this may have not been long enough to initiate such changes. In addition, no exercise interventions were used. Maximal strength improvements have been shown to be specific to the training stimulus (1) and therefore would

be unlikely to change despite reductions in pain. However, our data demonstrated that submaximal local muscular endurance was responsive to pain reductions. Dynamic muscular endurance improved by ~ 23% and isometric local muscular endurance increased by ~ 36%. Considering that normal activities of daily living rely very little on one's maximal lifting ability, our data demonstrate improvements in functional performance (i.e., improved submaximal endurance) may be obtained with a topical treatment consisting of a blend of cetylated fatty acids and menthol in patients with arthritis of the elbow or wrist.

PRACTICAL APPLICATIONS

Our data provide further support for the use of a topical cream consisting of a blend of cetylated fatty acids and menthol in the treatment of patients with arthritis of the knee, elbow, and wrist. In the present investigation, we reported significant improvements in stair climbing ability, "up and go" performance, balance, range of motion, and reductions in pain in patients with knee OA, and significant improvements in dynamic and isometric local muscular endurance and a reduction in pain in patients with severe pain in the elbow and wrist. The changes were similar to what we had previously noted. In addition, the use of such topical treatment may allow patients to better exercise thereby helping to improve health and fitness. Strength and conditioning professionals who work with such populations may find it enhances workout capabilities.

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Table 1. Pain and Performance Changes in Patients with Knee OA during the One-Week Experimental Period.

Test	Pre	Post	Adjusted P value
Up & Go (s)	9.37 ± 2.9	8.22 ± 2.4	0.004*****
Stairs – Total Time (s)	14.85 ± 6.3	13.05 ± 5.3	0.004*****
Stairs – Ascending (s)	6.86 ± 2.0	5.99 ± 1.8	0.001*****
Stairs – Descending (s)	7.10 ± 4.4	6.19 ± 3.4	0.029*****
Anterior Reach – R (cm)	44.65 ± 7.7	50.30 ± 6.0	0.004*****
Anterior Reach – L (cm)	41.65 ± 9.0	49.90 ± 7.7	0.000*****
Step-down - R	13.80 ± 14.0	18.50 ± 18.8	0.109
Step-down - L	12.10 ± 15.2	16.30 ± 14.9	0.058
ROM – SUP Ext – R (^{o})	8.90 ± 5.1	6.90 ± 4.0	0.098
ROM – SUP Ext – L (^{o})	8.10 ± 3.7	5.60 ± 2.9	0.050*****
ROM – SUP Flex – R (^{o})	115.10 ± 8.0	120.20 ± 7.6	0.026*****
ROM – SUP Flex – L (^{o})	116.50 ± 6.6	120.00 ± 6.8	0.037*****
WOMAC – Pain	9.35 ± 3.4	5.00 ± 3.8	0.004*****
WOMAC – Stiffness	3.70 ± 1.8	2.40 ± 2.2	0.090
WOMAC – Function	30.55 ± 12.9	16.30 ± 15.0	0.036*****

***** = $P \leq 0.05$; R – right leg; L – left leg; Ext – extended knee and hip position; Flex – flexed knee and hip position

Table 2. Pain and Performance Changes in Patients with Elbow Arthritis during the One-Week Experimental Period.

Test	Pre	Post	Adjusted P value
ROM – Ext. (^{o}) - R	22.50 ± 7.3	21.88 ± 5.3	0.537
ROM – Ext. (^{o}) - L	22.88 ± 7.6	22.94 ± 6.7	0.927
ROM – Flexion (^{o}) - R	135.75 ± 9.8	139.25 ± 6.1	0.132
ROM – Flexion (^{o}) - L	137.88 ± 8.3	139.00 ± 7.3	0.219
Arm Curl (Repetitions) - R	25.50 ± 18.3	30.30 ± 20.9	0.012*****
Arm Curl (Repetitions) - L	21.63 ± 16.0	27.00 ± 17.7	0.001*****
1 RM Curl (kg)	11.08 ± 6.7	11.65 ± 6.4	0.339
Grip Strength (kg) - R	26.38 ± 10.4	26.40 ± 9.1	0.999
Grip Strength (kg) - L	24.56 ± 10.2	24.25 ± 8.0	0.744
ISOM Endurance (s)	90.45 ± 69.2	120.04 ± 80.3	0.002*****
ISOM Force (N)	228.88 ± 115.3	238.13 ± 116.8	0.308
Pain (0 – 4 Scale)	2.63 ± 1.1	1.5 ± 0.5	0.015*****

***** = $P \leq 0.05$; R – right leg; L – left leg; ext – fully extended elbow position; 1 RM – one-repetition maximum; ISOM - isometric

Table 3. Pain and Performance Changes in Patients with Wrist Arthritis during the One-Week Experimental Period.

Test	Pre	Post	Adjusted P value
Arm Curl (Repetitions) - R	18.40 ± 10.9	23.00 ± 12.2	0.009*****
Arm Curl (Repetitions) - L	16.80 ± 10.9	20.80 ± 11.2	0.001*****
1 RM Curl (kg)	9.31 ± 5.1	9.77 ± 4.9	0.332
Grip Strength (kg) - R	21.35 ± 8.9	21.65 ± 8.5	0.703
Grip Strength (kg) - L	19.65 ± 8.3	20.40 ± 7.6	0.304
ISOM Endurance (s)	68.87 ± 66.6	97.62 ± 79.5	0.002*****
ISOM Force (N)	190.70 ± 95.2	203.80 ± 107.8	0.067
Pain (0 – 4 Scale)	2.70 ± 0.8	1.5 ± 0.5	0.003*****

***** = $P \leq 0.05$; R – right leg; L – left leg; 1 RM – one-repetition maximum; ISOM – isometric