Use of Low Level of Continuous Heat as an Adjunct to Physical Therapy Improves Knee Pain Recovery and the Compliance for Home Exercise in Patients With Chronic Knee Pain: A Randomized Controlled Trial

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Abstract

Petrofsky, JS, Laymon, MS, Alshammari, FS, and Lee, H. Use of low level of continuous heat as an adjunct to physical therapy improves knee pain recovery and the compliance for home exercise in patients with chronic knee pain: a randomized controlled trial. *J Strength Cond Res* 30(11): 3107–3115, 2016—This study examined if the use of low level continuous heat (LLCH) wraps at home between physical therapy sessions at a clinic resulted in better therapy outcomes in patients with chronic knee pain. Fifty individuals with chronic nonspecific knee pain was randomly allocated to 2 groups: the LLCH group and the placebo group. All subjects underwent 1 hour of conventional physical therapy twice per week for 2 weeks at the outpatient clinic and they were asked to accomplish 1 hour of therapeutic exercise at home each day between sessions. The LLCH group applied LLCH knee wraps for 6 hours at home before home exercise while placebo group took a placebo ibuprofen. (This was done since placebo heat is impossible to use since subjects would notice that the wraps were cold) Before, during, and after intervention, pain intensity, active range of motion of the knee (AROM), knee strength, and home exercise compliance were measured. The LLCH group showed pain attenuation after 2 weeks of therapy sessions ($p \leq 0.05$). AROM and strength of the knee significantly improved over time compared to the placebo group. Home exercise compliance was significantly higher in the LLCH group than placebo group ($p \leq 0.05$). These results indicated that the use of LLCH as an adjunct to conventional physical therapy for chronic knee pain significantly improved pain attenuation and recovery of strength and movement in patients with chronic knee pain.

Key Words range of motion, strength, thermo therapy, home exercise

Introduction

After lower back injuries, knee injuries are one of the most common types of injuries in sports and seen in physical therapy (49,50). Anterior and posterior cruciate ligament tears are common and many require surgery (1,2). However, lesser injuries such as knee collateral ligament tears and meniscus tears are common (5). Injuries that involve strain and not total tears also require attention of athletic trainers and physical therapists (3). Therapy usually involves heat and stretching exercise to increase range of motion (ROM), and isometric exercise to improve strength in damaged tissue (3). Due to limitations imposed by insurance carriers, there are only limited clinic visits allowed and therapists usually prescribe a home program with daily exercise between in-clinic therapy sessions to continue the recovery process. If not completed at home, recovery is slow.

The health care system in the United States has been under increasing burden because of spiraling medical costs and an increase in people who do not have health insurance (11). Thus any kind of treatment that enhances recovery after injury will reduce medical costs, and decrease the burden on the health care system in the United States (9,11).

However, one problem encountered in physical therapy is the limitation on the duration and treatment sessions. For most injuries with a single diagnosis, only 3 weeks of physical therapy is allowed, consisting of 45–60 minutes of treatment 2–3 times per week. Therefore, part of the burden on treatment is placed on the patients by having them accomplish therapy at home, which consists of stretching and home exercise programs to accomplish every day to

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increase ROM and build muscle strength. Many times, however, patients do not accomplish these regimes because of severe pain so that home exercise compliance usually is very poor (10,12,15,43,45).

Heat is a common modality used in physical therapy (25–27,32–34,38,41). It is has been well demonstrated that it reduces pain and increases healing by increasing blood flow in tissue (20,44,51). Clinical use of heat packs usually involves only a 15-minute modality, whereas low-level continuous heat (LLCH) wraps can be left on for hours with little chance of a burn and deep heat penetration and a sustained increase in tissue blood flow (14,20,23,28,31,32,40).

Although heat is often used in a clinical setting, therapists send patients home to exercise without heat. Furthermore, consumers buy continuous low-level heat wraps on their own for self-care but rarely with professional therapy. It would seem that if heat increases healing and reduces pain, there would be better compliance for home stretching and exercise if heat was used at home. This, in turn, should increase healing and further reduce pain to allow people to go back to normal activities or work sooner, saving additional therapy and its costs. Therefore, subjects with nonspecific knee pain underwent 2 weeks of therapy with standard clinical outcomes of pain, ROM and strength testing, as well as compliance for their home exercise program. Here, half of the subjects used continuous low-level heat wraps at home before home exercise and stretching to test the hypothesis that using LLCH on the knee at home for 6 hours before home exercise and on days when clinic treatments were not given would (a) decrease knee pain and (b) allow for better compliance for home exercise programs.

Methods

Experimental Approach to the Problem

Patients with chronic nonspecific knee pain were randomly allocated to an LLCH group and a placebo group to see if there is an effect of LLCH as an adjunct to physical therapy for knee pain recovery and the compliance for home exercise. Data was collected at the outpatient clinic in Southern California between January 2014 and April 2015. All data were collected in the morning of each investigational day. The participants and the investigators who measured all outcome measurement were blinded.

Subjects

Fifty three patients with chronic nonspecific knee pain came to the physical therapy clinic were enrolled in the study. Subjects were included if (a) they had knee pain more than 3 months, (b) the pain was not caused by fractures or full tears, and (c) they did not undergo knee surgery within the past year. Patients with diagnosed diabetes and taking oral analgesics including opioids and muscle relaxants were excluded from the study.

Fifty-three patients with chronic nonspecific knee pain came to the physical therapy clinic in Southern California for treatment (age range 26–64 years). All subjects were diagnosed by an orthopedic surgeon. Three subjects who did not meet inclusion criteria were excluded from the study. Therefore, 50 patients with chronic knee pain who signed the informed consent were randomly divided into either the LLCH group ($n = 25$) or the placebo group ($n = 25$) using systematic random sampling. Nondescript knee pain had the following diagnostic criteria: generalized knee pain with no manual tests or imaging indicating ligamentous, tendon, meniscus, or muscle tear, diagnosis of chondromalacia, patellar tracking dysfunction, patella alta, generalized knee effusion secondary to arthritis, strains, or strains

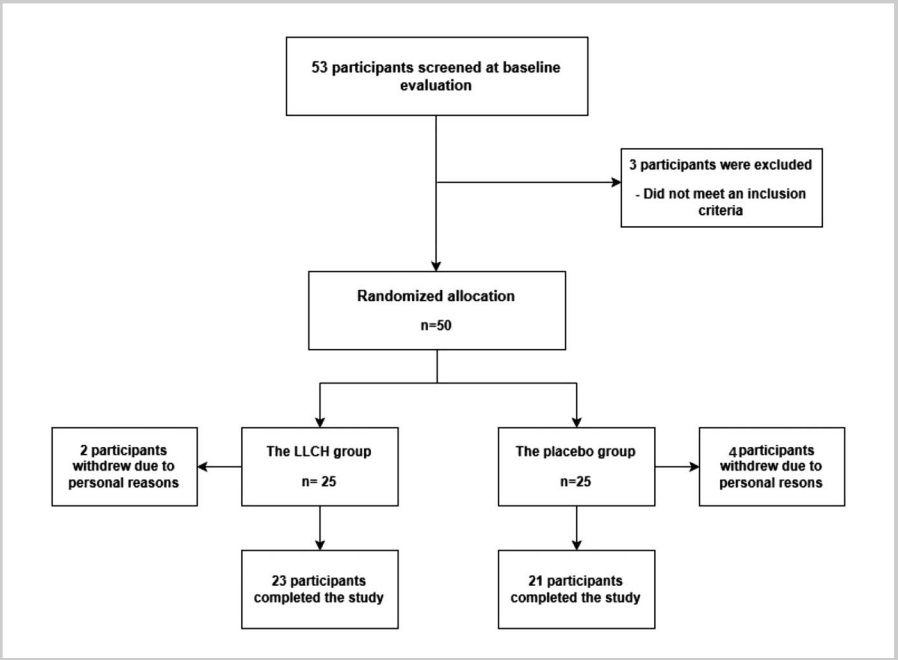

Figure 1. The progression of participants through the study. LLCH = low-level continuous heat.

Table 1. General characteristic of subjects.*

	LLCH group ($n = 23$)	Placebo group ($n = 21$)	p†
Age (y)	54.1 ± 11.0	54.5 ± 14.1	0.97
Height (cm)	169.5 ± 11.9	171.7 ± 9.7	0.69
Weight (kg)	90.4 ± 20.7	97.5 ± 20.1	0.67
Duration of pain (y)	1.5 ± 1.4	1.7 ± 1.05	0.75

*LLCH = low-level continuous heat.
†Independent t-test.

without compromise of supportive structures. Subjects were also matched by activity on a 5-point scale. Here, 0 was no activity and 5 was very active everyday with exercise. Only subjects who scored between 2 and 3 were accepted. Subjects were told they could not vary their activity during the study. Six subjects dropped out in the last week of the study for personal reasons leaving 23 subjects in the LLCH group and 21 subjects in the control (placebo) group (Figure 1). All subjects signed a statement of informed consent approved by the Solutions Institutional Review Board (IRB).

Procedures

All potential participants who met inclusion and exclusion criteria were provided with detailed information regarding the purpose, procedure, interventions, and potential risks of the study. If subjects agreed to proceed, they signed the informed consent form as approved by the Solutions IRB before they participated in the study. All procedures were also approved by the solutions IRB.

An initial evaluation and rehabilitation program was established which included a home exercise program. All subjects in the LLCH group were given a commercially available, over-the-counter, LLCH pack (ThermaCare; Pfizer, Inc., Kings Mountain, NC) which they would apply to their sore knee 6 hours before they performed their home exercise each day they were not in therapy. The control group took what they thought was ibuprofen but was a placebo dosage so that the placebo effect could be seen in this group. This was done because placebo heat is impossible to use, as subjects would notice that the wraps were cold.

All groups were evaluated each week. They were given home exercise and heat compliance logs and a visual analog scale (VAS) for pain to be filled out each night before exercise and, if they used heat, before and after the heat was applied. The exercises included exercises for extending ROM to stimulate synovial fluid activation via capsular stimulation. Synovial fluid activation means the production of new fluid and removal of older fluid deficient in oxygen and nutrients. Articular cartilage depends on synovial fluid for nutrients because it does not have direct blood supply. Active ROM also stimulates muscle activity to help with lymphatic flow to decrease generalized effusion. The physical therapist filled out the knee outcome survey activities of daily living scale at the beginning and at end of the study and interviewed the subject to ensure that they did not change their activity levels at each therapy session. To improve intrarater reliability, a physical therapist with 8-year experience took all outcome measurements.

Interventions

All subjects underwent 1 hour of conventional physical therapy which included thermotherapy, joint mobility, stretching, isometric exercise, and postural exercise twice per week for 2 weeks at the outpatient clinic. In addition to that, they were asked to accomplish 1 hour of therapeutic exercise which included stretching and exercise at home each day they were not in the clinic. The LLCH group was asked to apply LLCH wrap on the knee for 6 hours, whereas the placebo control group was asked to take a placebo ibuprofen before they started home exercise every day to decrease pain.

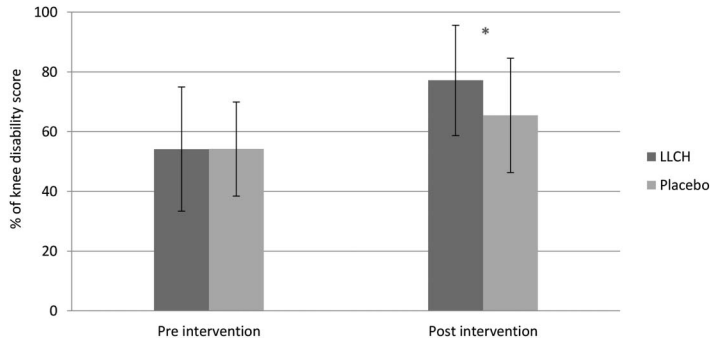

Figure 2. Disability score in pre- and postintervention in the LLCH and placebo groups. LLCH = low-level continuous heat. *Significant difference between the LLCH and placebo groups.

Outcome Measurement

Knee pain was measured by a VAS. The VAS score was used to measure subjective pain at each therapy session and on each day at home. Subjects placed a vertical mark across a 10-cm horizontal line such that the closer they marked near the 10-cm point,

Table 2. Outcome variables at pre- and postintervention and mean change.*†

Group/variables	Preintervention	Postintervention	Mean changes (CI)
Disability score (%)			
LLCH	54.26 ± 20.75	77.35 ± 18.44‡§	23.09 (16.28 to 29.9)
Placebo	54.38 ± 15.71	65.52 ± 19.19‡	11.14 (5.09 to 17.20)
Subjective pain (mm)			
LLCH	41.20 ± 28.38	16.10 ± 19.01‡§	−25.09 (−35.61 to −14.57)
Placebo	45.80 ± 21.78	34.96 ± 24.84‡	−10.79 (−24.37 to 2.80)
Strength (flexion)			
LLCH	8.04 ± 0.93	10.04 ± 1.49‡§	2.00 (1.45 to 2.55)
Placebo	7.76 ± 1.41	8.52 ± 1.69‡	0.76 (0.27 to 1.26)
Strength (extension)			
LLCH	9.09 ± 1.65	10.43 ± 1.27‡	1.35 (0.85 to 1.85)
Placebo	8.47 ± 1.66	9.43 ± 1.43‡	0.95 (0.40 to 1.50)
AROM (flexion, degree)			
LLCH	110.26 ± 19.62	127.70 ± 17.04‡§	17.43 (8.88 to 25.99)
Placebo	109.98 ± 17.04	119.15 ± 14.27‡	9.17 (3.14 to 15.20)
AROM (extension, degree)			
LLCH	−7.22 ± 5.47	−2.95 ± 3.35‡	4.27 (2.80 to 5.75)
Placebo	−7.72 ± 7.91	−4.12 ± 4.39‡	3.60 (0.03 to 7.18)

*CI = confidence interval; LLCH = low-level continuous heat; AROM = active range of motion.
†Values are mean ± *SD*.
‡Significant difference between pre and post intervention ($p \leq 0.05$).
§Significant difference in changes from pre- to post intervention between LLCH and placebo group ($p \leq 0.05$).

the greater was their pain. The first step in calculating the combined pain scale was to multiply the visual analog score by 10. Thus, the score would go from 0 to 100. Hundred on this scale was extremely painful, whereas 0 indicated no pain. Each scale was on a separate paper so that they were not biased by previous marks.

A knee outcome survey activities-of-daily-living scale was used before and at the end of the study. The survey evaluated the effect of knee pain on activities of daily living. If the score was 60, there was no impairment. The survey has been validated and previously reported. A score of 0 indicated maximum impairment (6). The score was normalized to a 100% scale.

A digital goniometer was used to measure active range of motion (AROM) in the knee (Baseline digital goniometer, number 12-1027; Fabrication Enterprises, Inc., White Plains, NY, USA). Knee AROM was determined with the patient in the sitting position. The subjects flexed and extended the knee within a range without pain, and AROM was measured.

Strength was assessed by the same physical therapist so that the measures would have better reliability. Measures of strength of the knee flexors and extensor muscles were on a standard 5-point scale with plus and minus for 2, 3, 4, and 5 (0, no contraction; 1, visible contraction with no movement; 2, movement with no gravity; 3, movement against gravity only; 4, movement against gravity, moderate resistance; 5, movement against full resistance). However, for purpose of data

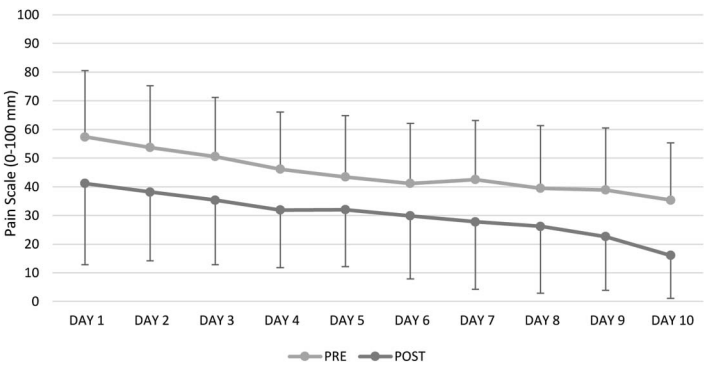

Figure 3. Subject self-reported pain scale between before and after LLCH warp applied over time in the LLCH group. LLCH = low-level continuous heat.

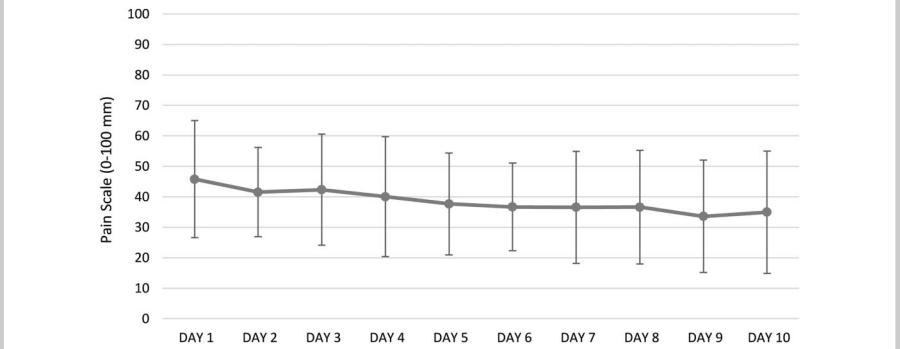

Figure 4. Subject self-reported pain scale over time in the placebo group.

entry to avoid plus and minus measures, this scale was converted to a 12-point numeric scale as follows;

0 = 0
1 = 1
2− = 2
2 = 3
2+ = 4
3− = 5
3 = 6
3+ = 7
4− = 8
4 = 9
4+ = 10
5− = 11
5 = 12

Subjects kept a home exercise log. They scored, for each day they participated in home exercise, as a percentage score for how much they exercised. For example, if they exercised for 30 minutes and were to exercise 60 minutes, they would score 50%. Subjects kept a home heat compliance log. They scored, for each day they participated and used heat, as a percentage score for how much they left the heat on. For example, if they used heat for 3 hours and were to use if for 6 hours, they would score 50%.

The heat that was applied was a ThermaCare heat wrap (Pfizer, Inc., Kings Mountain, NC). These are continuous therapy products that produce a fairly constant skin temperature of 41 ± 0.5° C. The temperature is controlled by a flow-limited reaction controlled by small holes drilled in the cover of the wrap with a laser to maintain constant flow of oxygen. The wraps come to temperature in about 15 minutes and maintain temperature for 8–12 hours.

Sample Size Estimation

G-Power 3.1.9.2 software was used to calculate the sample size required so that a reasonable expectation would be likely to detect an expected effect size of 0.8 between the 2 independent groups. A sample size of 42, with 21 participants per group was required to show statistical significance when clinically significant differences between the groups were present. Additional participants were recruited to provide for unanticipated dropout.

Statistical Analyses

Data were summarized as means and *SD*s using SPSS for Windows version 22.0 (IBM, Armonk, NY, USA). The characteristics of the subjects were compared between the LLCH group and placebo group using independent *t*-test for the quantitative variables and χ^2 for independence for categorical variables. The normality of the outcome variables at baseline and postintervention was examined using one-sample Kolmogorov-Smirnov test. Since the distribution of these variables was normal, all outcome measurements were compared between the 2 groups using 1-tailed independent *t*-test. In each group, comparisons between pre- (baseline) and postintervention (2 weeks) were assessed using the paired *t*-test. The level of significance was set at $p \leq 0.05$.

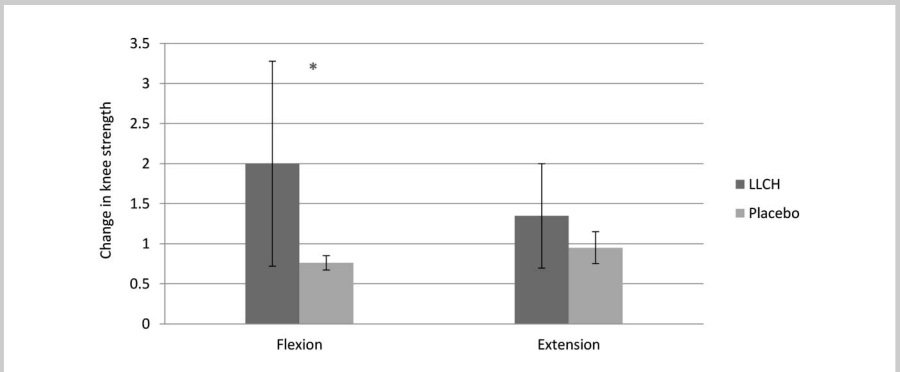

Figure 5. The change in strength between pre- and postintervention for knee flexion and extension in the LLCH and placebo groups. LLCH = low-level continuous heat. *Significant difference between the LLCH and placebo groups.

Results

Two subjects from the LLCH group and 4 from the placebo group withdrew because of

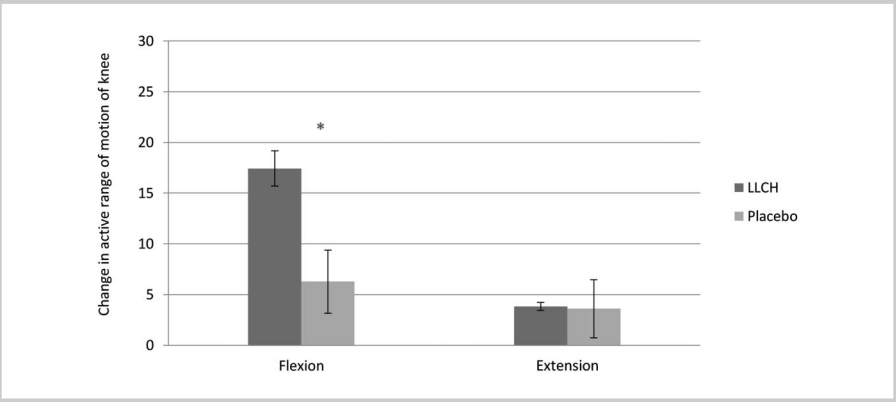

Figure 6. The change in active range of motion between pre- and postintervention for knee flexion and extension in the LLCH and placebo groups. LLCH = low-level continuous heat. *Significant difference between the LLCH and placebo groups.

personal reasons. Therefore, 44 participants (23 in the LLCH group and 21 in the placebo group) completed the study. There were no significant differences in general characteristics between the LLCH group and placebo group (Table 1).

Both groups had a significant decrease in disability (increase in the score) associated with the 2 weeks of therapy ($p < 0.001$). However, the reduction in the disability score was greater ($p = 0.01$) in the LLCH group. There was no significant difference in the score in both groups pretherapy ($p = 0.968$), whereas postintervention (2 weeks) the LLCH group showed a significant improvement of 23 points and the increase in the placebo group was 11.28 points ($p = 0.010$, Figure 2 and Table 2).

The pain intensity as self-reported by the subjects is shown in Figures 3 and 4 for the LLCH and placebo groups, respectively. As can be seen in Figure 3, for the LLCH group, subjective pain was less each day for the 10 days of home measures ($p \leq 0.05$). In addition, LLCH wrap always caused a significant reduction in knee pain each day before home exercise. Comparing Figures 3 and 4 (control subjects), there was a greater reduction in pain over the 10 sessions before heat in the LLCH group (Figure 3 and Table 2) compared with the placebo group (Figure 4 and Table 2). The reduction in pain before heat was significantly greater after the second day of heat in the LLCH group compared with the placebo group ($p < 0.01$). Each day heat was applied, there was a reduction in pain that was significant ($p < 0.01$).

The change in strength for flexion and extension of knee before and after the 2 weeks of conventional physical therapy and home exercise is shown in Figure 5. Both groups showed significant increase of strength between pre- and postintervention, but the increase in strength in the LLCH group was more than double (248.2%) that of the placebo group over the 2 weeks for flexion ($p < 0.001$) but not significant for extension ($p = 0.272$, Table 2).

Active range of motion in the knee joint without pain significantly increased in both groups pre- and postintervention ($p < 0.01$). However, the increase in AROM in the knee joint was significantly greater in the LLCH group than that measured in the placebo group over the 2 weeks for flexion but not significant for the extension ($p = 0.021$ and $p = 0.905$, respectively, Figure 6 and Table 2).

The compliance for intervention between the groups was not significantly different ($p = 0.078$, Figure 7) but the compliance for home exercise program in both groups was significantly different. The exercise completion of the LLCH group was significantly higher than the placebo group by over 25.8%. ($p = 0.045$, Figure 7).

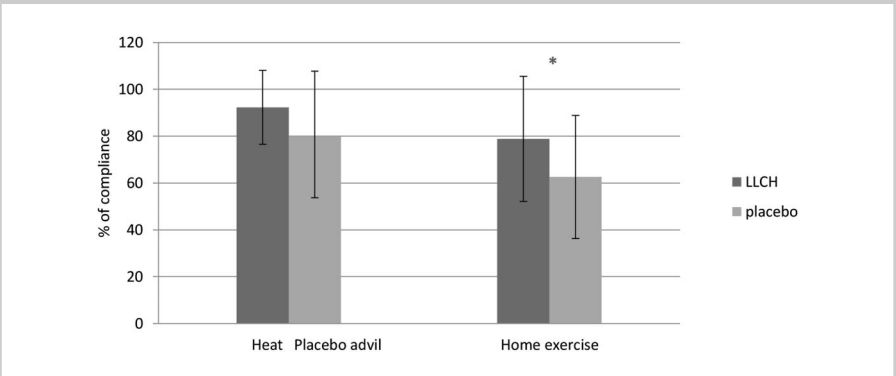

Figure 7. The change in intervention and home exercise compliance between pre- and postintervention in the LLCH and placebo groups. LLCH = low-level continuous heat. *Significant difference between the LLCH and placebo groups.

Discussion

When high-temperature heat, such as hydrocollator heat pack, is applied to the skin, only local heating of the skin is offered and there is poor deep tissue penetration (25,39).

These packs must be carefully watched because they can damage the skin. In contrast, continuous low-level heat packs that are left on for hours

reduce pain in minutes (17,18,20,28,31,40,47) and increase blood flow to deep tissues (29,30,35,36,46,52). The greater tissue temperature and blood flow increases the rate of healing of tissue (37,38). Numerous studies have shown safe and beneficial effects of continuous low-level heat (7,16,21). The effect of heat on pain is well documented.

Pain is mediated in the body through nerve endings via purine receptors. Adenosine triphosphate release triggers pain in muscle, skin, joints, and other organs (42). These puregenic receptors are modulated by the transient receptor potential cation channel subfamily V (TRPV) family of receptors, notably TRPV1 receptors, that are sensitive to heat. Therefore, heat has the effect of reducing pain. Continuous low-level heat wraps have been shown to reduce back and neck pain in numerous clinical studies (4,6,28,30,38,47).

In addition to pain relief, heat increases blood flow to tissues. These same TRPV1 receptors and in addition the TRPV4 voltage-gated calcium channels increase influx of calcium into vascular endothelial cells. This in turn activates the enzyme endothelial nitric oxide synthetase allowing it to convert L-argine to L-citrulline and release nitric oxide, a potent vasodilator.

This increase in blood flow helps remove toxins from tissues and promotes healing. Healing is also increased by increasing tissue temperature. Tissue metabolism doubles for about every 3° C increase in temperature. Thus, any increase in temperature would promote faster healing by raising metabolism. For joints such as the knee, tissue temperature is that of a shell tissue and usually about 30° C. This is 7° C less than that of the core and as such, heat has the potential to quadruple metabolism. This, then, would be a major contributor to healing.

In the present investigation, recovery from nonspecific knee injuries was faster if home continuous low-level heat wraps were used before stretching and exercise. While this population was undergoing physical therapy, they were able to exercise more at home, regaining strength faster and increasing flexibility with the use of home heat therapy. This is not to say that therapy was not successful. Data clearly shows that therapy was beneficial in the control group. But therapy conducted by physical therapists or treatments by trainers on athletes can only be a few hours a day. The advantage of using continuous low-level heat wraps is that they last for more than 8 hours, reducing pain so that exercise can be continued with less pain at home and healing is faster.

In the present investigation, the group that received LLCH showed significantly more pain attenuation each day during the application of heat to the knee. Furthermore, the reduction in pain was coupled with a significantly better compliance for home exercise and greater increase in ROM, strength, and the knee outcome survey activities of daily living compared with the control group. These findings, then, are in line with previous reports showing the increased healing power and lower pain associated with heat therapy. Other studies have examined the effect of heat on knee and gait quality with heating of the knee (4,19,22,24). Removing pain alone would not increase strength. But the reduced pain would allow more exercise and the exercise then would be effective in increasing strength and ROM as seen here.

The difference in the present investigation is that heat was used as an adjunct to conventional physical therapy; in other words, normal exercise in clinic intervention was used for the 2-week period. The use of LLCH was meant to increase the efficiency of home exercise. Home exercise has been considered to have only a minimal effect on recovery from knee pain (13,48). Due to pain, compliance for home exercise is usually poor (10,12,15,43,45). Here, heat significantly improved the home exercise compliance and outcomes of therapy, which should shorten therapy in patients with knee pain. In the present study, where LLCH and exercise were used together, although not combined with physical therapy, heat and exercise were synergistic, as seen here, in improving gait and knee function (8). Although people with arthritis and anterior cruciate ligament and meniscus injuries were excluded, other studies have shown that the use of heat benefits decreasing pain and increasing mobility in these individuals as well and should also help in the clinical setting.

Practical Applications

For the coach or trainer, this study suggests a different approach. In addition to using whirlpool and other heat modalities after exercise, recovery from injuries and overexertion of muscles may be faster if 8-hour continuous low-level heat wraps are used at home. This will reduce pain and increase healing and maintain flexibility in soft tissue to optimize return to activity.

References

1. Alentorn-Geli, E, Mendiguchia, J, Samuelsson, K, Musahl, V, Karlsson, J, Cugat, R, and Myer, GD. Prevention of anterior cruciate ligament injuries in sports-Part I: Systematic review of risk factors in male athletes. *Knee Surg Sports Traumatol Arthrosc* 22: 3–15, 2014.
2. Alentorn-Geli, E, Mendiguchia, J, Samuelsson, K, Musahl, V, Karlsson, J, Cugat, R, and Myer, GD. Prevention of non-contact anterior cruciate ligament injuries in sports. Part II: Systematic review of the effectiveness of prevention programmes in male athletes. *Knee Surg Sports Traumatol Arthrosc* 22: 16–25, 2014.
3. Campbell, JD. The evolution and current treatment trends with anterior cruciate, posterior cruciate, and medial collateral ligament injuries. *Am J Knee Surg* 11: 128–135, 1998.
4. Giombini, A, Di Cesare, A, Di Cesare, M, Ripani, M, and Maffulli, N. Localized hyperthermia induced by microwave diathermy in osteoarthritis of the knee: A randomized placebo-controlled double-blind clinical trial. *Knee Surg Sports Traumatol Arthrosc* 19: 980–987, 2011.
5. Holzer, LA, Leithner, A, and Holzer, G. Surgery versus physical therapy for meniscal tear and osteoarthritis. *N Engl J Med* 369: 677, 2013.
6. Irrgang, JJ, Snyder-Mackler, L, Wainner, RS, Fu, FH, and Harner, CD. Development of a patient-reported measure of function of the knee. *J Bone Joint Surg Am* 80: 1132–1145, 1998.
7. Kesiktas, N, Paker, N, Erdogan, N, Gulsen, G, Bicki, D, and Yilmaz, H. The use of hydrotherapy for the management of spasticity. *Neurorehabil Neural Repair* 18: 268–273, 2004.

8. Kim, H, Suzuki, T, Saito, K, Kim, M, Kojima, N, Ishizaki, T, Yamashiro, Y, Hosoi, E, and Yoshida, H. Effectiveness of exercise with or without thermal therapy for community-dwelling elderly Japanese women with non-specific knee pain: A randomized controlled trial. *Arch Gerontol Geriatr* 57: 352–359, 2013.
9. Kjaer, HO, Dimcevski, G, Hoff, G, Olesen, F, and Ostergaard, L. Recurrence of urogenital *Chlamydia trachomatis* infection evaluated by mailed samples obtained at home: 24 weeks' prospective follow up study. *Sex Transm Infect* 76: 169–172, 2000.
10. Kjaer, SK. [Screening for cervix cancer–where are we going?]. *Ugeskr Laeger* 162: 3015, 2000.
11. Kjaergaard, GH and Laursen, JO. [Osteonecrosis of a knee joint in a young man with IDDM]. *Ugeskr Laeger* 162: 4663–4664, 2000.
12. Langberg, H, Skovgaard, D, Asp, S, and Kjaer, M. Time pattern of exercise-induced changes in type I collagen turnover after prolonged endurance exercise in humans. *Calcif Tissue Int* 67: 41–44, 2000.
13. Lankhorst, NE, van Middelkoop, M, van Trier, YD, van Linschoten, R, Koes, BW, Verhaar, JA, and Bierma-Zeinstra, SM. Can we predict which subjects with patellofemoral pain syndrome are more likely to benefit from exercise therapy: A secondary explorative analysis of a randomized controlled trial. *J Orthop Sports Phys Ther*: 1–24, 2015.
14. Laymon, M, Petrofsky, J, McKivigan, J, Lee, H, and Yim, J. Effect of heat, cold, and pressure on the transverse carpal ligament and median nerve: A pilot study. *Med Sci Monit* 21: 446–451, 2015.
15. Lederer, K, Godt, A, Howes, PB, Kjaer, K, Als-Nielsen, J, Lahav, M, Wegner, G, Leiserowitz, L, and Weissbuch II. Crystalline self-assembly into monolayers of folded oligomers at the air-water interface. *Chemistry* 6: 2173–2183, 2000.
16. Lewis, SE, Holmes, PS, Woby, SR, Hindle, J, and Fowler, NE. Short-term effect of superficial heat treatment on paraspinal muscle activity, stature recovery, and psychological factors in patients with chronic low back pain. *Arch Phys Med Rehabil* 93: 367–372, 2012.
17. Lin, CC, Chiang, YS, and Lung, CC. Effect of infrared-C radiation on skin temperature, electrodermal conductance and pain in hemiparetic stroke patients. *Int J Radiat Biol* 91: 42–53, 2015.
18. Lin, JH, Chiang, YH, and Chen, CC. Research strategies for pain in lumbar radiculopathy focusing on acid-sensing ion channels and their toxins. *Curr Top Med Chem*, 2015.
19. Lorig, K, Feigenbaum, P, Regan, C, Ung, E, Chastain, RL, and Holman, HR. A comparison of lay-taught and professional-taught arthritis self-management courses. *J Rheumatol* 13: 763–767, 1986.
20. Malanga, GA, Yan, N, and Stark, J. Mechanisms and efficacy of heat and cold therapies for musculoskeletal injury. *Postgrad Med* 127: 57–65, 2015.
21. Mayer, JM, Mooney, V, Matheson, LN, Erasala, GN, Verna, JL, Udermann, BE, and Leggett, S. Continuous low-level heat wrap therapy for the prevention and early phase treatment of delayed-onset muscle soreness of the low back: A randomized controlled trial. *Arch Phys Med Rehabil* 87: 1310–1317, 2006.
22. Mazzuca, SA, Page, MC, Meldrum, RD, Brandt, KD, and Petty-Saphon, S. Pilot study of the effects of a heat-retaining knee sleeve on joint pain, stiffness, and function in patients with knee osteoarthritis. *Arthritis Rheum* 51: 716–721, 2004.
23. Nadler, SF, Steiner, DJ, Erasala, GN, Hengehold, DA, Hinkle, RT, Beth Goodale, M, Abeln, SB, and Weingand, KW. Continuous low-level heat wrap therapy provides more efficacy than Ibuprofen and acetaminophen for acute low back pain. *Spine (Phila Pa 1976)* 27: 1012–1017, 2002.
24. Ochiai, S, Watanabe, A, Oda, H, and Ikeda, H. Effectiveness of thermotherapy using a heat and steam generating sheet for cartilage in knee osteoarthritis. *J Phys Ther Sci* 26: 281–284, 2014.
25. Petrofsky, J, Alshahmmari, F, Yim, JE, Hamdan, A, Lee, H, Neupane, S, Shetye, G, Moniz, H, Chen, WT, Cho, S, Pathak, K, Malthane, S, Shenoy, S, Somanaboina, K, Alshaharani, M, Nevgi, B, Dave, B, and Desai, R. The interrelationship between locally applied heat, ageing and skin blood flow on heat transfer into and from the skin. *J Med Eng Technol* 35: 262–274, 2011.
26. Petrofsky, J, Bains, G, Prowse, M, Gunda, S, Berk, L, Raju, C, Ethiraju, G, Vanarasa, D, and Madani, P. Dry heat, moist heat and body fat: Are heating modalities really effective in people who are overweight?. *J Med Eng Technol* 33: 361–369, 2009.
27. Petrofsky, J, Batt, J, Bollinger, JN, Jensen, MC, Maru, EH, and Al-Nakhli, HH. Comparison of different heat modalities for treating delayed-onset muscle soreness in people with diabetes. *Diabetes Technol Ther*, 2011.
28. Petrofsky, J, Batt, J, Bollinger, JN, Jensen, MC, Maru, EH, and Al-Nakhli, HH. Comparison of different heat modalities for treating delayed-onset muscle soreness in people with diabetes. *Diabetes Technol Ther* 13: 645–655, 2011.
29. Petrofsky, J, Berk, L, and Al-Nakhli, H. The influence of autonomic dysfunction associated with aging and type 2 diabetes on daily life activities. *Exp Diabetes Res* 657103: 2012, 2012.
30. Petrofsky, J, Berk, L, Alshammari, F, Lee, H, Hamdan, A, Yim, JE, Patel, D, Kodawala, Y, Shetye, G, Chen, WT, Moniz, H, Pathak, K, Somanaboina, K, Desai, R, Dave, B, Malthane, S, Alshaharani, M, Neupane, S, Shenoy, S, Nevgi, B, Cho, S, and Al-Nakhli, H. The effect of moist air on skin blood flow and temperature in subjects with and without diabetes. *Diabetes Technol Ther* 14: 105–116, 2012.
31. Petrofsky, J, Berk, L, Bains, G, Khowailed, IA, Hui, T, Granado, M, Laymon, M, and Lee, H. Moist heat or dry heat for delayed onset muscle soreness. *J Clin Med Res* 5: 416–425, 2013.
32. Petrofsky, J, Goraksh, N, Alshammari, F, Mohanan, M, Soni, J, Trivedi, M, Lee, H, Hudlikar, AN, Yang, CH, Agilan, B, Pai, N, Chindam, T, Murugesan, V, Eun Yim, J, and Katrak, V. The ability of the skin to absorb heat; the effect of repeated exposure and age. *Med Sci Monit* 17: CR1–8, 2011.
33. Petrofsky, J, Paluso, D, Anderson, D, Swan, K, Yim, JE, Murugesan, V, Chindam, T, Goraksh, N, Alshammari, F, Lee, H, Trivedi, M, Hudlikar, AN, and Katrak, V. The contribution of skin blood flow in warming the skin after the application of local heat; the duality of the Pennes heat equation. *Med Eng Phys* 33: 325–329, 2011.
34. Petrofsky, JS. A device to measure heat flow through the skin in people with diabetes. *Diabetes Technol Ther* 12: 737–743, 2010.
35. Petrofsky, JS, Alshahmmari, F, Lee, H, Hamdan, A, Yim, JE, Shetye, G, Neupane, S, Somanaboina, K, Pathak, K, Shenoy, S, Dave, B, Cho, S, Chen, WT, Nevgi, B, Moniz, H, Alshaharani, M, Malthane, S, and Desai, R. Reduced endothelial function in the skin in Southeast Asians compared to Caucasians. *Med Sci Monit* 18: CR1–8, 2012.
36. Petrofsky, JS, Berk, L, Alshammari, F, Lee, H, Hamdan, A, Yim, JE, Kodawala, Y, Patel, D, Nevgi, B, Shetye, G, Moniz, H, Chen, WT, Alshaharani, M, Pathak, K, Neupane, S, Somanaboina, K, Shenoy, S, Cho, S, Dave, B, Desai, R, Malthane, S, and Al-Nakhli, H. The interrelationship between air temperature and humidity as applied locally to the skin: The resultant response on skin temperature and blood flow with age differences. *Med Sci Monit* 18: CR201–208, 2012.
37. Petrofsky, JS, Lawson, D, Berk, L, and Suh, H. Enhanced healing of diabetic foot ulcers using local heat and electrical stimulation for 30 min three times per week. *J Diabetes* 2: 41–46, 2010.
38. Petrofsky, JS, Lawson, D, Suh, HJ, Rossi, C, Zapata, K, Broadwell, E, and Littleton, L. The influence of local versus global heat on the healing of chronic wounds in patients with diabetes. *Diabetes Technol Ther* 9: 535–544, 2007.
39. Petrofsky, JS and Laymon, M. Heat transfer to deep tissue: The effect of body fat and heating modality. *J Med Eng Technol* 33: 337–348, 2009.
40. Petrofsky, JS, Laymon, M, and Lee, H. Effect of heat and cold on tendon flexibility and force to flex the human knee. *Med Sci Monit* 19: 661–667, 2013.

41. Petrofsky, JS, Lohman, E, Suh, HJ, Garcia, J, Anders, A, Sutterfield, C, Grabicki, J, and Khandge, C. Determination of the conductive heat exchange of the skin in relation to environmental temperature. *J Appl Res Clin Exp Ther* 6: 157–169, 2006.

42. Puchalowicz, K, Tarnowski, M, Baranowska-Bosiacka, I, Chlubek, D, and Dziedziejko, V. P2X and P2Y receptors-role in the pathophysiology of the nervous system. *Int J Mol Sci* 15: 23672–23704, 2014.

43. Schollen, E, Kjaergaard, S, Legius, E, Schwartz, M, and Matthijs, G. Lack of Hardy-Weinberg equilibrium for the most prevalent PMM2 mutation in CDG-Ia (congenital disorders of glycosylation type Ia). *Eur J Hum Genet* 8: 367–371, 2000.

44. Shahzad, Y, Louw, R, Gerber, M, and du Plessis, J. Breaching the skin barrier through temperature modulations. *J Control Release* 202C: 1–13, 2015.

45. Sigsgaard, T, Bonefeld-Jorgensen, EC, Kjaergaard, SK, Mamas, S, and Pedersen, OF. Cytokine release from the nasal mucosa and whole blood after experimental exposures to organic dusts. *Eur Respir J* 16: 140–145, 2000.

46. Song, CW. Effect of local hyperthermia on blood flow and microenvironment: A review. *Cancer Res* 44: 4721s–4730s, 1984.

47. Stark, J, Petrofsky, J, Berk, L, Bains, G, Chen, S, and Doyle, G. Continuous low-level heatwrap therapy relieves low back pain and reduces muscle stiffness. *Phys Sportsmed* 42: 39–48, 2014.

48. van der Heijden, RA, Lankhorst, NE, van Linschoten, R, Bierma-Zeinstra, SM, and van Middelkoop, M. Exercise for treating patellofemoral pain syndrome. *Cochrane Database Syst Rev* 1. CD010387, 2015.

49. Werner, BC, Gwathmey, FW Jr, Higgins, ST, Hart, JM, and Miller, MD. Ultra-low velocity knee dislocations: Patient characteristics, complications, and outcomes. *Am J Sports Med* 42: 358–363, 2014.

50. Werner, BC, Hadeed, MM, Gwathmey, FW Jr, Gaskin, CM, Hart, JM, and Miller, MD. Medial injury in knee Dislocations: What are the common injury patterns and surgical outcomes?. *Clin Orthop Relat Res*, 2014.

51. Willems, E, Knigge, U, Jorgensen, H, Kjaer, A, and Warberg, J. Effect of blockade of postsynaptic H1 or H2 receptors or activation of presynaptic H3 receptors on catecholamine-induced stimulation of ACTH and prolactin secretion. *Eur J Endocrinol* 142: 637–641, 2000.

52. Yim, J, Petrofsky, J, Berk, L, Daher, N, and Lohman, E. Differences in endothelial function between Korean-Asians and Caucasians. *Med Sci Monit* 18: CR337–343, 2012.